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Symposium on Rehabilitation in Cardiovascular Disease

PHILIP R. LEE, M.D. AND SERGIUS BRYNER, M.D.

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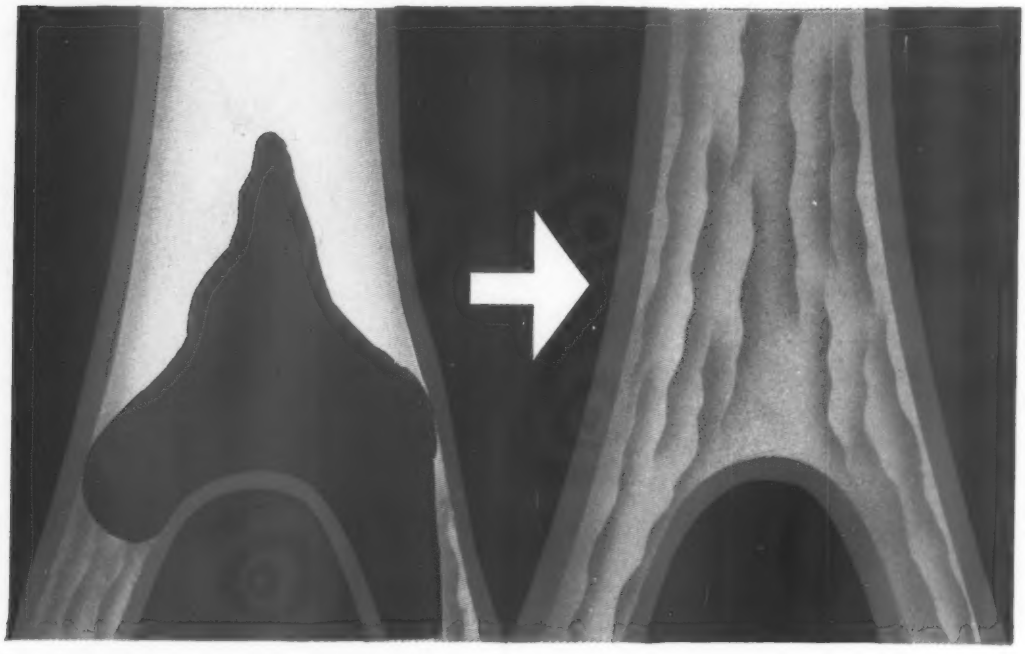

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References: **1.** Tandowsky, R. M.: Personal communication. **2.** Parsons, W. B.: *Curr. Therapeut. Res. 2*:137 (May) 1960. **3.** Thompson, C. E.: Personal communication. **4.** Biben, L. H.; Kurstin, W., and Protas, M.: Personal communication. **5.** Hobbs, T. G.: Personal communication.

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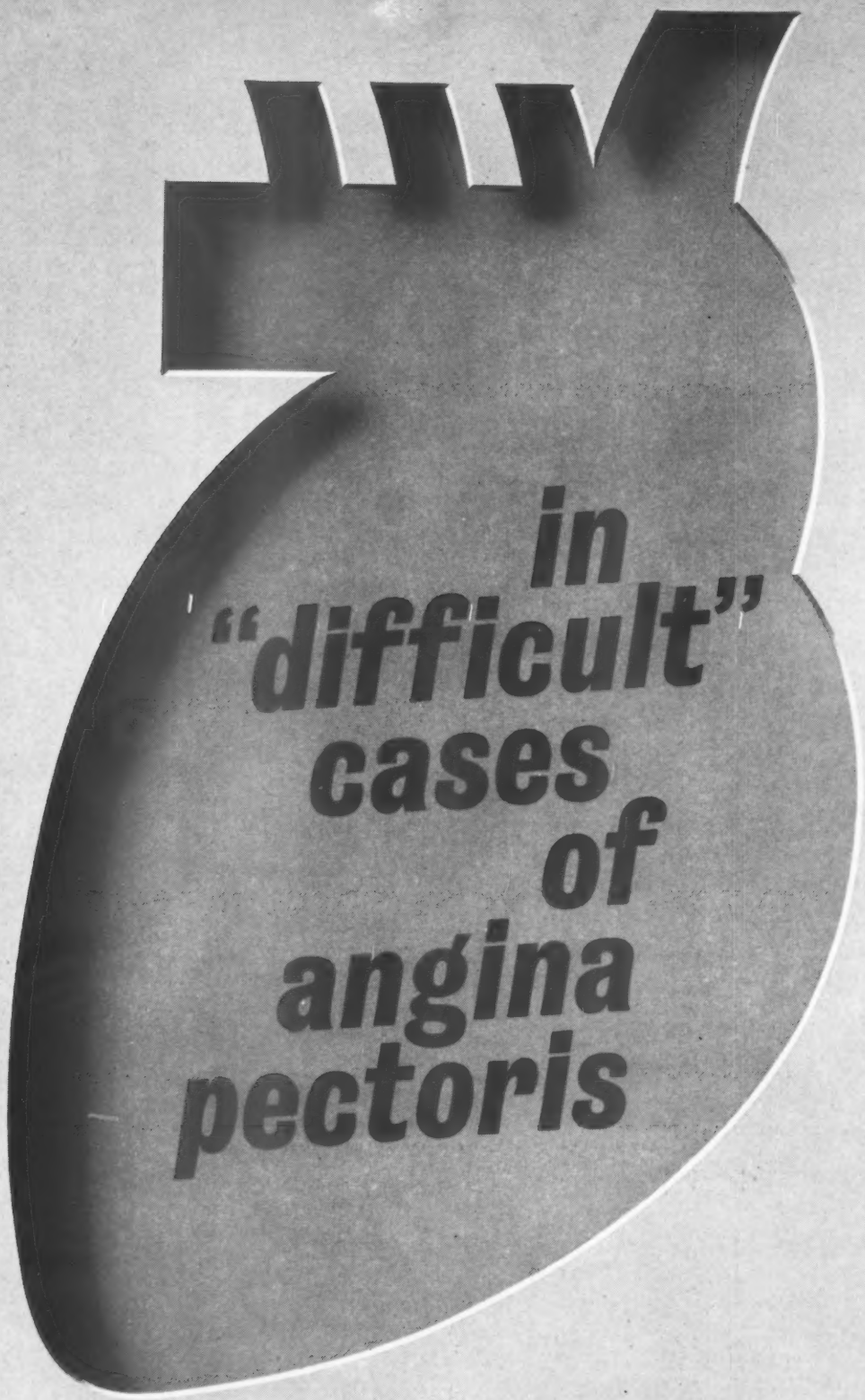

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The American Journal of Cardiology

Volume VII MARCH 1961 Number 3

CONTENTS

Symposium on Rehabilitation in Cardiovascular Disease

Introduction 315
PHILIP R. LEE AND SERGIUS BRYNER

Rehabilitation of the Cardiac Patient 317
BRYAN WILLIAMS AND PAUL D. WHITE

From extensive experience and with fundamental insight cardiac rehabilitation means "a return of the patient to the fullest life possible in every sphere of life within the limits imposed by his heart disease." From extensive experience and with profound insight Williams and White propose a simple bill of rights for the cardiac patient which all physicians can profitably peruse. Other helpful hints on smoking, diet, intercourse, physical activity and work are thoughtfully included.

Cardiovascular Responses to Exercise Concerned in Rehabilitation of Cardiac Patients. Physiologic Considerations 320
ERNST JOKL

Homeostasis and heterostasis (disengagement from homeostasis) are two key physiologic problems upon which rests the understanding of cardiovascular rehabilitation. The latter process is primarily determined by the integrated nature of the discharge pattern of impulses from the central nervous system. Data from trained and untrained subjects are explained on the basis of these two fundamental processes

Exercise Testing of Cardiac Patients in Evaluating Work Potential 330
ROBERT M. LEVENSON AND DONALD R. SPARKMAN

Using a motor-driven treadmill to test physical fitness of cardiac patients for work, these investigators observed good correlation in 75 per cent of their patients between clinical estimations of disability and these results. They recommend simple forms of exercise tests which could provide the physician with a sounder basis for advising his cardiac patients.

Rehabilitation of the Child with Congenital Heart Disease 335
PATRICK A. ONGLEY AND JAMES W. DUSHANE

Many everyday problems concerned with the rehabilitation of children with congenital heart disease are discussed.

Survival and Rehabilitation in Coronary Occlusion 340
ARTHUR M. MASTER

Master paints an optimistic picture for the continued survival and successful rehabilitation of patients with coronary occlusion and supports his view with up-to-date statistics. Work and unstructured leisure are his talisman for improving the health of heart cases. He denies that coronary occlusion is precipitated by work or is an occupational hazard for physicians.

Contents continued on page 7

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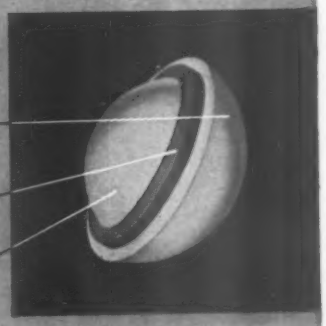

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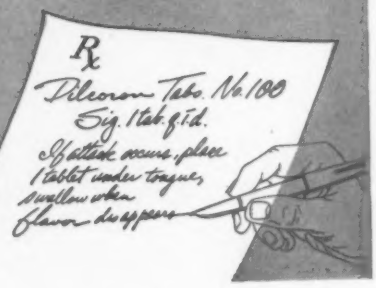

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CONTENTS continued—March 1961

VOLUME SEVEN NUMBER THREE

Rehabilitation and Employment of Industrial Workers with Cardiovascular Disease . 350
WILLIAM E. R. GREER

Employment of 219 industrial employees with cardiovascular disease over eight years has not shown increased mortality, excessive absenteeism or apparent increase in insurance risk.

Returning the Farmer with Cardiac Disease to Work 354
RICHARD P. GRIPE, BENJAMIN Z. KLATCH, PHILIP W. ROTHROCK, WILFORD H. M. MORRIS AND ROBERT L. EICHHORN

The farmer with cardiac disease poses rehabilitation problems because of the nature of his work and certain social traits. For the physician concerned with cardiac farmers this article offers a comprehensive approach to the proper management of such patients; for others it offers an interesting commentary of the value of a sociologically oriented study of environmental factors, community resources and adequate medical help for farmers with cardiac disease.

Prognosis for Rehabilitation of the Older Adult and the Aged Hemiplegic Patient . . 365
MIECZYSLAW PESZCZYNSKI

The prognosis for successful rehabilitation of the aged hemiplegic patient depends in great part on the general cardiovascular status. Prolonged bowel incontinence and flexion contracture of the hemiplegic knee indicate a poorer outlook for rehabilitation. Much more study of the psychologic factors is indicated.

Potential Reversibility of the Hemiplegic Posture. Results of Reconstructive Surgical Procedures 370
WALTER J. TREANOR AND GEORGE H. REIFENSTEIN

Reconstructive surgery to correct muscular imbalances in adults with spastic hemiparesis was performed in 184 patients with varying success. The rationale for such surgery is that the greatly improved kinetic balance between antagonistic muscle groups produces better motor recovery by a more balanced proprioceptive input to spinal synapses.

Psychiatric Considerations of Cerebral Vascular Disease 379
SAUL H. FISHER

Cerebral vascular disease represents a massive assault on the organism with multiple psychiatric implications. These mental factors are discussed from the viewpoints of clinical management and effective rehabilitations.

Clinical Studies

The Effect of Guanethidine in the Treatment of Hypertension. A Study of Twenty-Five Patients 386
MAUDE STEVENSON, NELSON GOODMAN, DAVID FINKELSTEIN AND SAMUEL BELLET

Although a useful supplement to other hypotensive agents, guanethidine alone has little place in the treatment of hypertension.

Contents continued on page 9

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CONTENTS continued—March 1961

VOLUME SEVEN NUMBER THREE

The Hypotensive Effects of Chlorothiazide and Hydrochlorothiazide. A Critical Comparison 392
J. MARION BRYANT, NATALIO SCHVARTZ, MARIA ROQUE, LUCIAN FLETCHER, HARRISON FERTIG AND DAVID P. LAULER

Chlorothiazide and hydrochlorothiazide with and without reserpine demonstrate a significant hypotensive effect. Side effects are infrequent.

Clinical Observations on the Diuretic Effect of Hydrochlorothiazide 396
GABOR CZONICZER, EDWARD BURWELL, JOHN NILES, RAPHAEL REIDER, JOSEPH ROBINSON AND BENEDICT F. MASSELL

In the therapeutic dosage range the relative amounts of hydrochlorothiazide and chlorothiazide producing the same diuretic effect is generally 1 to 10, in children as well as adults.

Effect of Reserpine and Syrosingopine on the Rate and Contractility of the Human Heart 404
WILHELM RAAB, HANS MARCHET AND HERMAN C. HERRLICH

Prolonged administration of small doses of reserpine and syrosingopine lowered the blood pressure and reduced the heart rate and, in these subjects, exerted a negative inotropic effect on the normal heart, presumably due to depletion of myocardial norepinephrine. An opposite reaction of the isometric period in two subjects was attributed to the coexisting hypersensitivity to catecholamine of catecholamine-depleted cardiovascular tissues.

Experimental Study

Angina Pectoris. IV. Clinical and Experimental Difference Between Ischemia with S-T Elevation and Ischemia with S-T Depression 412
ALI EKMEKCI, HIDEO TOYOSHIMA, JAN K. KWOCZYNSKI, TERUO NAGAYA AND MYRON PRINZMETAL

A well conceived research design, classic in its simplicity, permits the investigators to demonstrate primary S-T depression and primary S-T elevation in animals and to correlate these changes with similar ones in human beings. S-T segment elevation is associated with more severe ischemia than S-T segment depression. Primary S-T depression also occurs with nonischemic conditions due to chemical alterations. It is in no way at variance with the principle of reciprocity or other fundamental laws of electrocardiography.

Historical Milestones

Description of Circulatory Collapse and Coronary Thrombosis in the Fifth Centry A.D. by Caelius Aurelianus. 427
RUDOLPH E. SIEGEL

Abstracts from the fifth century book "On Acute Diseases and on Chronic Diseases" by Caelius Aurelianus provide a detailed account of the cardiologic knowledge of this era, particularly pertaining to circulatory collapse and coronary thrombosis.

Contents continued on page 11

in coronary artery disease

with or without angina

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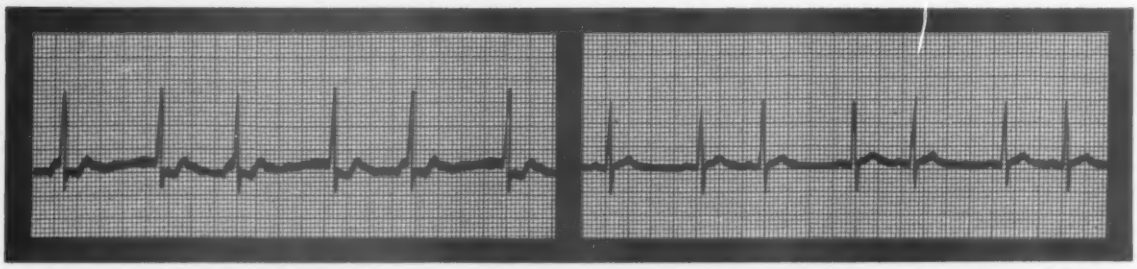
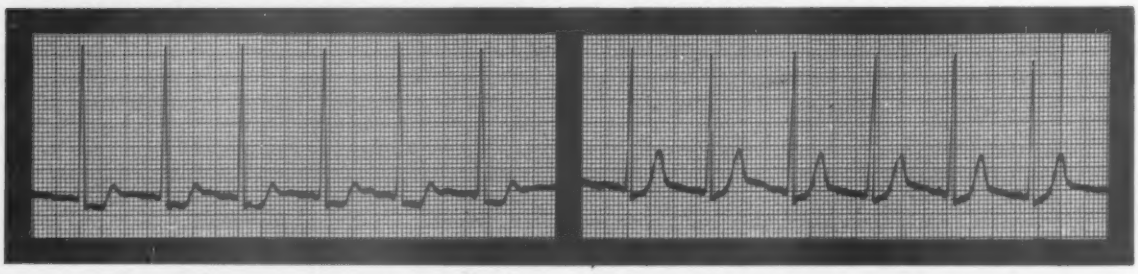
the patient with angina*



before Peritrate—S-T depression after standard exercise in anginal patient with no history of infarction.

after Peritrate (20 mg., administered 4 hours before exercise test). S-T segment near normal.

the postcoronary patient without angina*



before Peritrate—Abnormal ECG response to standard exercise in postinfarction patient without angina.

after Peritrate (20 mg., administered 90 minutes before exercise test). S-T segment near normal.

*Electrocardiograms and case histories on file in the Medical Department, Warner-Chilcott Laboratories.

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CONTENTS continued—March 1961

VOLUME SEVEN NUMBER THREE

Case Reports

Congenital Heart Disease Associated with Congenital Hypofibrinogenemia. Report of a Case Subjected to Corrective Surgery 432
JESSE F. MINNIS, JR. AND E. HARRISON GRIFFIN

The first case of congenital hypofibrinogenemia and congenital heart disease (pulmonic stenosis and partial anomalous pulmonary venous drainage) is reported together with suggestions for the surgical management of such cases. Bleeding and clotting tests are recommended as screening tests for hematologic defects before surgery.

Cor Triatriatum. Successful Diagnosis and Surgical Correction in a Three Year Old Girl 436
RAY C. ANDERSON AND RICHARD L. VARCO

This is a report of the first successful correction of a severe cor triatriatum in a three year old girl. Early diagnosis and corrective surgery is mandatory in this congenital defect.

Ventricular Tachycardia Responding Solely to Digitalis Therapy. 441
RICHARD J. GREENWOOD AND DAVID FINKELSTEIN

Intravenous deslanoside produced sinus rhythm in a sixty year old man with ventricular tachycardia.

Intractable Ventricular Tachycardia. Unusual Mode of Conversion to Normal Rhythm Following Intravenous Procaine Amide 445
RAYMOND J. KOKOWICZ

A total of 3,940 mg. of procaine amide injected intravenously over an eighty minute period converted a paroxysmal ventricular tachycardia of twenty-eight days' duration to sinus rhythm.

Persistent Ventricular Tachycardia. Report of a Case Successfully Treated with Very Large Intraveous Doses of Procaine Amide 449
H. COLLIER WRIGHT AND ROBERT K. DAVIS

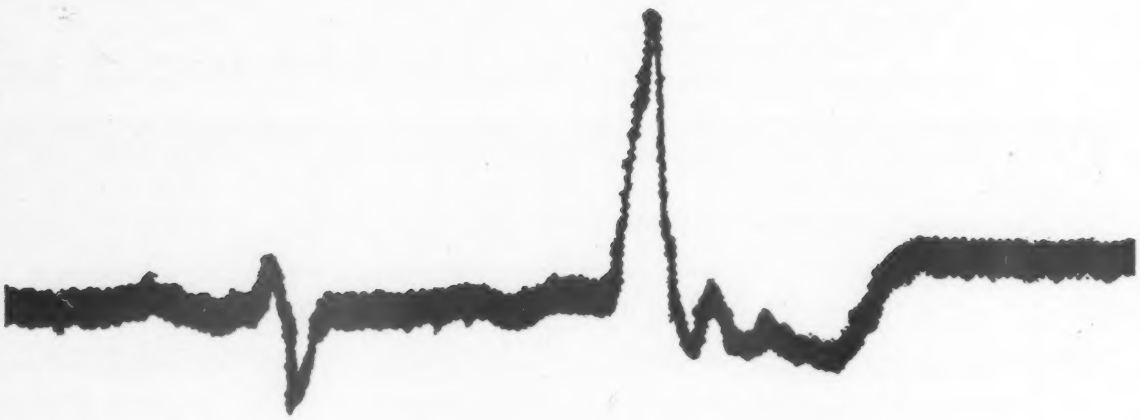
Large repeated doses of procaine amide successfully converted ventricular tachycardia to sinus rhythm.

Diagnostic Shelf

Graphic Expression of the Palpatory and Auscultatory Signs of A-V Fistula 454
MORTON EINHORN, RAYMOND E. REICH AND ALDO A. LUISADA

A graphic demonstration of the palpable thrill and auditory bruit in an A-V fistula of the popliteal vessels.

Contents continued on page 13



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Workmen's Compensation for the Cardiac 458
Letters to the Editor 464
Book Reviews 466
College News 469

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Index to Advertisers on pages 51 and 52

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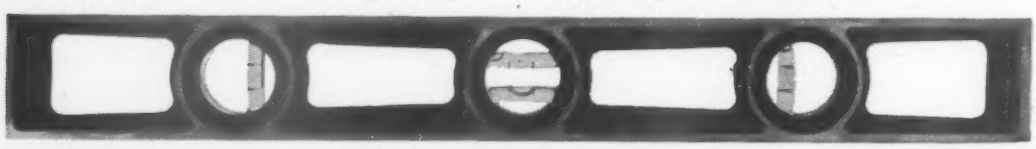

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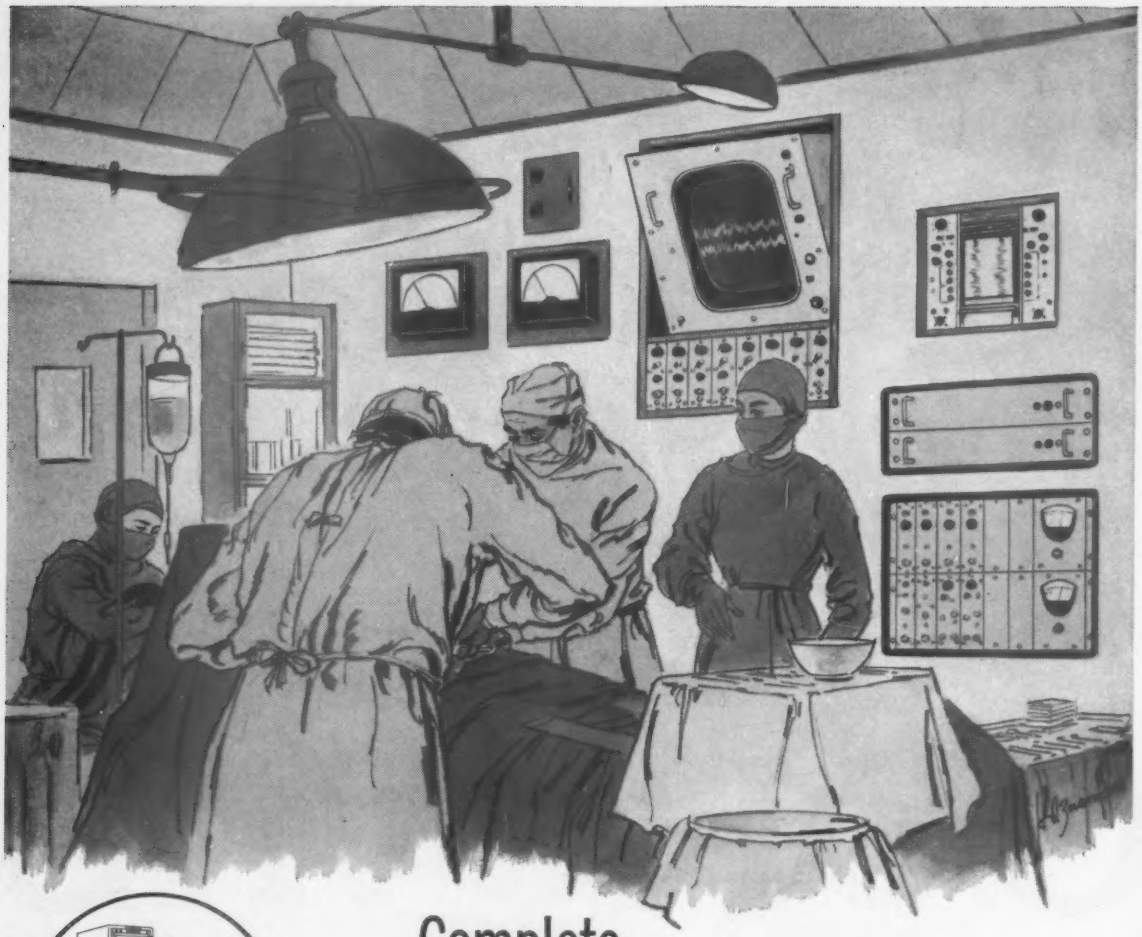

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Even in frank edema,
give it just *once daily*
ENDURON™
(METHYCLOTHIAZIDE, ABBOTT)
Each single daily dose
provides 24 full hours
of potent diuretic–
antihypertensive action
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Longest acting of

all available thiazides

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(In practical terms,

here's what Enduron's longer duration

means to you):

Dosage once a day, every day. Even in frank edema, once daily is all you need. Easy for patient to remember and stick to, easy for you to supervise.

No therapeutic gap between doses. Round the clock effectiveness. Your first dose provides good diuretic and hypotensive action that's sustained right up to the time next day's dose takes over.

Peak natruresis at 10 mg. level. Maximum sodium output occurs with each single 10 mg. dose. Natruresis remains well above control (i.e., undosed) level more than 24 hours. Larger single doses give no added effect, aren't needed.

Enhanced potassium-sparing effect. Enduron's single daily dose causes but a temporary single peak of potassium loss (compared to multiple daily peaks with multiple-dose thiazides). Basic ratio of sodium excretion versus potassium is enhanced, too. Potassium depletion is rarely seen.

ENDURON is a distinctive analogue of the thiazide family, created by Abbott, and available under no other trade name. Usual adult dose is only 2.5 to 10 mg. once daily; this low milligram dosage provides the security of a very safe therapeutic ratio. Supplied in 5 mg. (No. 6812) and 2.5 mg. (No. 6827) grooved tablets. Literature promptly supplied upon request to Abbott Laboratories, North Chicago, Ill.

BIBLIOGRAPHY 1. Ford, R. V., Clinical-Pharmacologic Investigation of Methyclothiazide, a New Oral Diuretic; Comparative Clinical Effects of Hydrochlorothiazide and Methyclothiazide, Current Therap. Res., 2:422-430, Sept., 1960. 2. Bryant, J. M., Schwartz, N., Fletcher, L., Jr., Fertig, H., Schwartz, M. S., McDermott, J. D., Quan, R., Clinical Studies of the Anti-hypertensive Effects of a New Benzothiadiazine Diuretic, submitted for publication.

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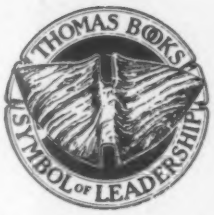

NEW BOOKS FOR THE CARDIOLOGIST PUBLISHED IN JANUARY, FEBRUARY AND MARCH 1961

SURGICAL DISEASES OF THE LUNG *by* **Buford H. Burch,** *Patton State Hospital, Patton, Calif., and* **Arthur C. Miller,** *College of Medical Evangelists, Loma Linda, Calif.* The short journey through this book will be a pleasant one for all physicians interested in lung diseases. The authors have stated their attitudes as briefly and as pointedly as possible—setting down what they believe to be the correct and most promising method of dealing with surgical diseases of the lung. *Included are diagnostic hints and "tricks of the trade"* so often referred to as good judgment; what to do for the patient before a diagnosis is established; how and when to proceed when a diagnosis has been made. *Pub. Feb. '61, 144 pp., 60 il., $8.50.*

CHEMISTRY AND THERAPY OF CHRONIC CARDIOVASCULAR DISEASE *by* **Richard J. Jones** *and* **Louis Cohen,** *both of Univ. of Chicago.* This book should be in the hands of every physician who treats the patient with heart disease. The authors review the chemical basis for the pathogenesis and therapy of three common complications of much chronic cardiovascular diseases—congestive heart failure, thrombosis, and arteriosclerosis. *Pub. March '61 (Amer. Lec. Living Chemistry)*

THE TREATMENT OF HYPERTENSION *by* **Sir George White Pickering, William Ian Cranston,** *and* **Michael Andrew Pears,** *all of Univ. of Oxford.* The patient is a whole organism, with a mind, as yet mysterious in its working, and a body partly so. Each patient presents a problem of greater or lesser complexity which the physician must try to solve. THE TREATMENT OF HYPERTENSION represents an integration of experimental knowledge with clinical wisdom in the cause of the hypertensive patient and his everyday problems. *How to* see the problem more fully, to solve it wisely, and to serve the best interests of the patient are all covered here. *Pub. March '61, 192 pp., 70 il. (Amer. Lec. Living Chemistry), $7.00.*

HENRY STANLEY PLUMMER: A Diversified Genius *by* **Fredrick A. Willius,** *The Mayo Clinic.* In a warm, intimate account Dr. Willius relives one of the highlights of his life—his many years of close professional association with Dr. Henry Stanley Plummer. Portrayed here is the very being of an unusual and talented pioneer in medicine —a great physician, a master of the science and art of medicine, a teacher surpassed by few, and a learned scientist in many fields. *Pub. Jan. '61, 80 pp., 15 il., $4.50.*

FUNCTIONAL BEHAVIOR OF THE MICROCIRCULATION *by Benjamin W. Zweifach, New York Univ.* This stimulating book covers an area only sketchily covered in most textbooks and curricula. It is a realistic appraisal of modern principles of blood-tissue exchange, tissue injury, and systemic disturbances such as shock and hypertension. Emphasis throughout is on the close correlation between structure and function. *Pub. March '61, (Amer. Lec. in Physiology)*

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Since linoleic acid is the principal polyunsaturated fatty acid in the vegetable oils which lower blood cholesterol, there seems to be no doubt that linoleic acid is the key factor in reducing serum cholesterol through diet. The facts are clearly stated in a recent JAMA editorial:

> "It is accepted generally that specific alteration in the diet will lower the concentration of cholesterol in the blood. The most effective results to date have been achieved by increasing consumption of polyunsaturated fatty acids, particularly linoleic acid ...they must replace rather than supplement some of the saturated fats and oils already in the diet."[2]

Very recent research indicates that use of Emdee Margarine in place of other spreads and shortenings may significantly contribute to reduction of serum cholesterol in diabetic patients,[1] as it has been observed to do in other patient groups.[3,4]

Emdee Margarine contains significantly more linoleic acid than any other margarine—including those promoted as "pure corn oil margarines." And, published scientific reports[3,4,5] attest to the value of Emdee Margarine in cholesterol-lowering diets. To date, no comparable studies with other margarines have been published.

REFERENCES:
1. Alterman, S. L.: Postgrad. Med. *28*:112 (Aug.) 1960.
2. Pollack, H.: J.A.M.A. *172*:1164 (Mar. 12) 1960.
3. Terman, L. A.: Geriatrics *14*:111 (Feb.) 1959.
4. Boyer, P. A., Jr.; Lowe, J. T.; Gardier, R. W., and Ralston, J. D.: J.A.M.A. *170*:257 (May 16) 1959.
5. Jolliffe, N.; Rinzler, S. H., and Archer, M.: Am. J. Clin. Nutrition *7*:451, 1959.

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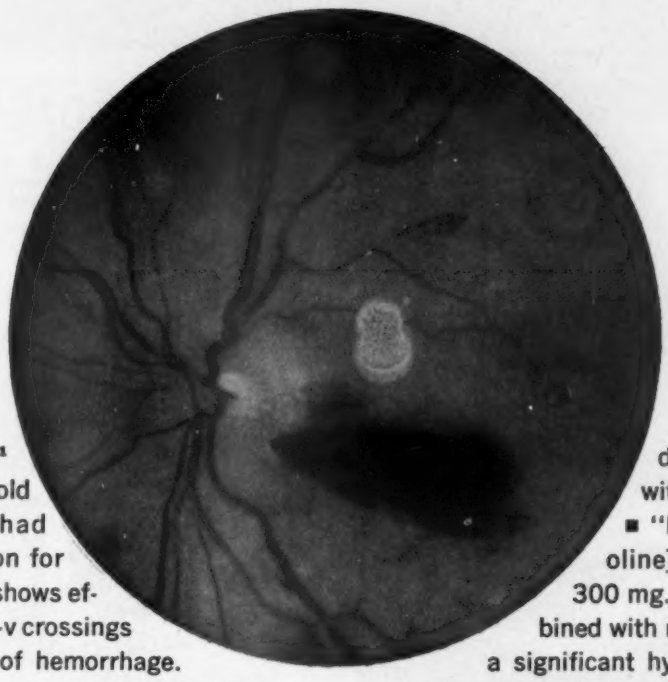

AS IN THIS CASE:[1] Fundus of 62-year-old female who has had severe hypertension for many years. Photo shows effect of pressure at a-v crossings and various types of hemorrhage.

■ When you see eyeground changes like this—with such hypertensive symptoms as dizziness and headache—your patient is a candidate for Serpasil-Apresoline. With this combination the antihypertensive action of Serpasil complements that of Apresoline to bring blood pressure down to near-normal levels in many cases. Side effects can be reduced to a minimum, since Apresoline is effective in lower dosage when given with Serpasil.

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1. Bedell, A. J.: Clin. Symposia 9:135 (Sept.-Oct.) 1957.
2. Lee, R. E., Seligman, A. M., Goebel, D., Fulton, L. A., and Clark, M. A.: Ann. Int. Med. 44:456 (March) 1956.

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1. Baer, S. [illegible] A.M.A. 167:704, June 7, 1958.
2. Master, K. M.: Disease-a-Month, Chicago, Yr. Bk. Pub., Mar. 1960, p. 13.

Full range of oral and parenteral dosage forms—

COUMADIN* (warfarin sodium) is available as: Scored tablets—2 mg., lavender; 5 mg., peach; 7½ mg., yellow; 10 mg., white; 25 mg., red. Single Injection Units—one vial, 50 mg., and one 2 cc. ampul Water for Injection; one vial, 75 mg., and one 3 cc. ampul Water for Injection.

Average Dose: Initial, 40-60 mg. For elderly and/or debilitated patients, 20-30 mg. Maintenance, 5-10 mg. daily, or as indicated by prothrombin time determinations.

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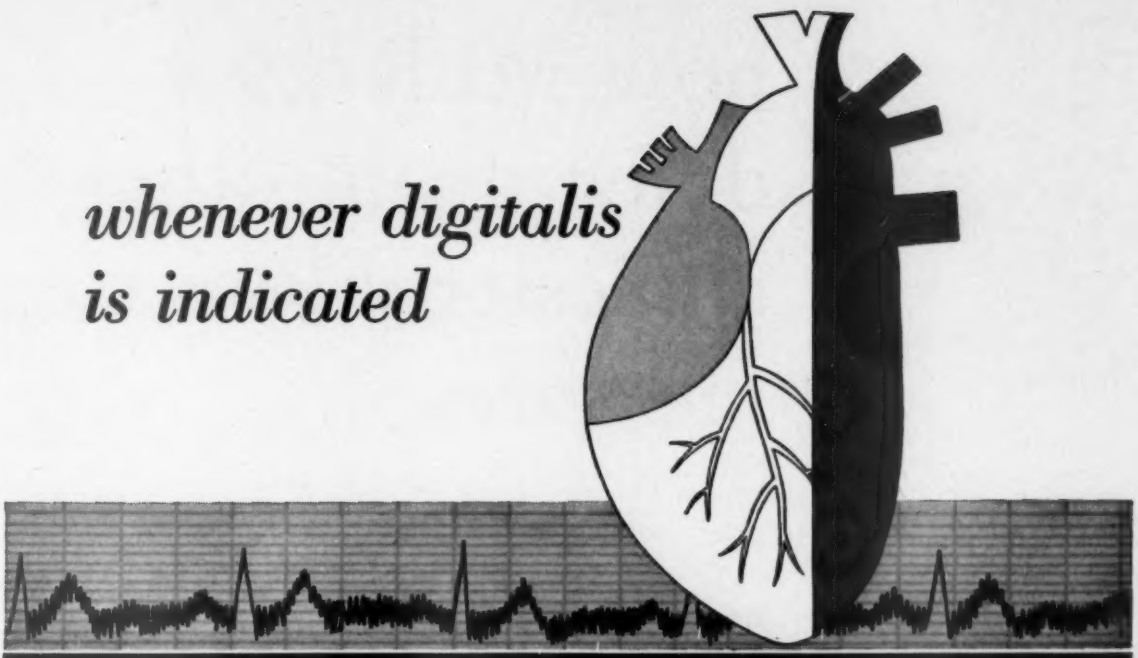

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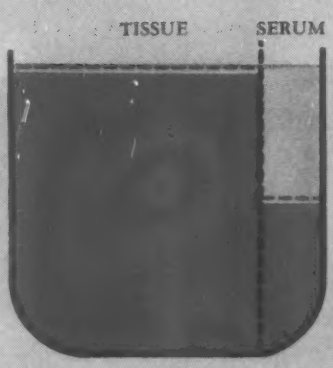
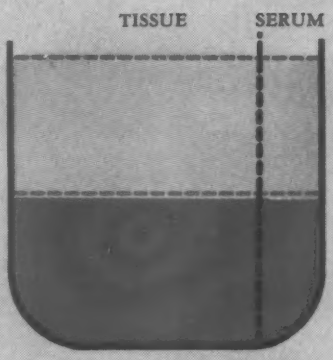
how MER/29 differs from other cholesterol-lowering measures . . .

effect on body pool of cholesterol



OTHER MEASURES

There is no evidence that tissue cholesterol is reduced even in the face of serum cholesterol reduction.



MER/29

Studies in patients have demonstrated a reduction of approximately 40% of *tissue* cholesterol, as well as a significant reduction of the *total* sterol pool.

. . . the first cholesterol-lowering agent to inhibit the formation of cholesterol within the body, reducing both tissue and serum cholesterol

. . . the only specific cholesterol-lowering agent: no demonstrable interference with other vital biochemical processes reported to date; toleration and absence of toxicity established by more than 2 years of clinical investigation

. . . convenient dosage: one 250 mg. capsule daily before breakfast

...and how these differences can benefit your patients

particularly those with high cholesterol levels, coronary artery disease, and generalized atherosclerosis

MER/29 REDUCES CHOLESTEROL IN 8 OUT OF 10 PATIENTS: MER/29 reduces both serum and tissue cholesterol, *irrespective of diet.* Although some physicians prefer to use MER/29 in conjunction with controlled diets, cholesterol can be reduced successfully without such limitation.

CONCURRENT BENEFITS REPORTED IN SOME PATIENTS: In angina patients, some of the concurrent benefits reported include decreased incidence and severity of attacks, improved ECG patterns, diminished nitroglycerin dependence, and increased sense of well-being.

DIRECT, SPECIFIC CHOLESTEROL-LOWERING ACTION WITH MER/29: Some agents used to reduce cholesterol have other important primary effects — such as hormonal or vasodilator action. The primary, the *only* known function of MER/29 is to reduce cholesterol.

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SUPPLIED: Bottles of 30 pearl gray capsules.

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For cardiovascular patients–a smooth, balanced action that lifts depression as it calms anxiety...rapidly and safely

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In contrast to such "seesaw" effects, Deprol lifts depression as it calms anxiety – both at the same time.

Acts swiftly–the patient often feels better, sleeps better, within two or three days. Unlike most other antidepressant drugs, Deprol relieves the patient quickly – often within two or three days.

Acts safely – no danger of hypotension. Deprol does not cause hypotension, tachycardia, jitteriness, or liver toxicity. It can be safely administered with basic cardiovascular therapy.

Dosage: Usual starting dose is 1 tablet q.i.d. When necessary, this may be gradually increased up to 3 tablets q.i.d.
Composition: 1 mg. 2-diethylaminoethyl benzilate hydrochloride (benactyzine HCl) and 400 mg. meprobamate.
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Deprol

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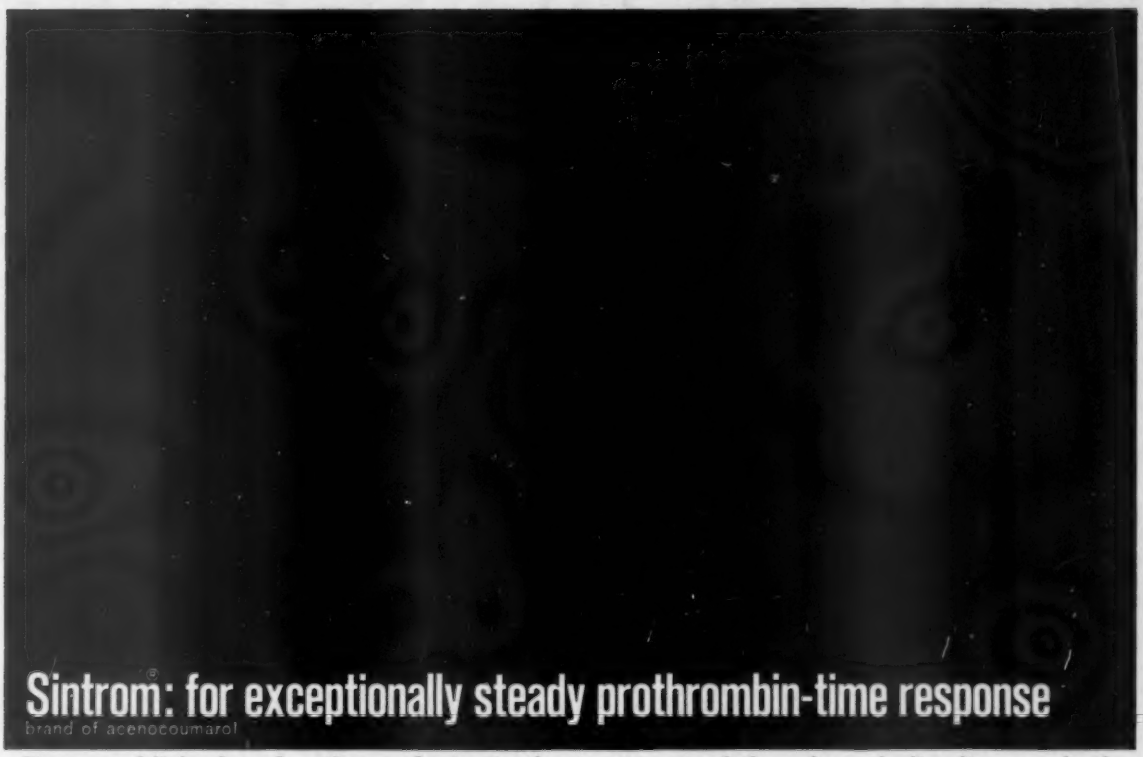

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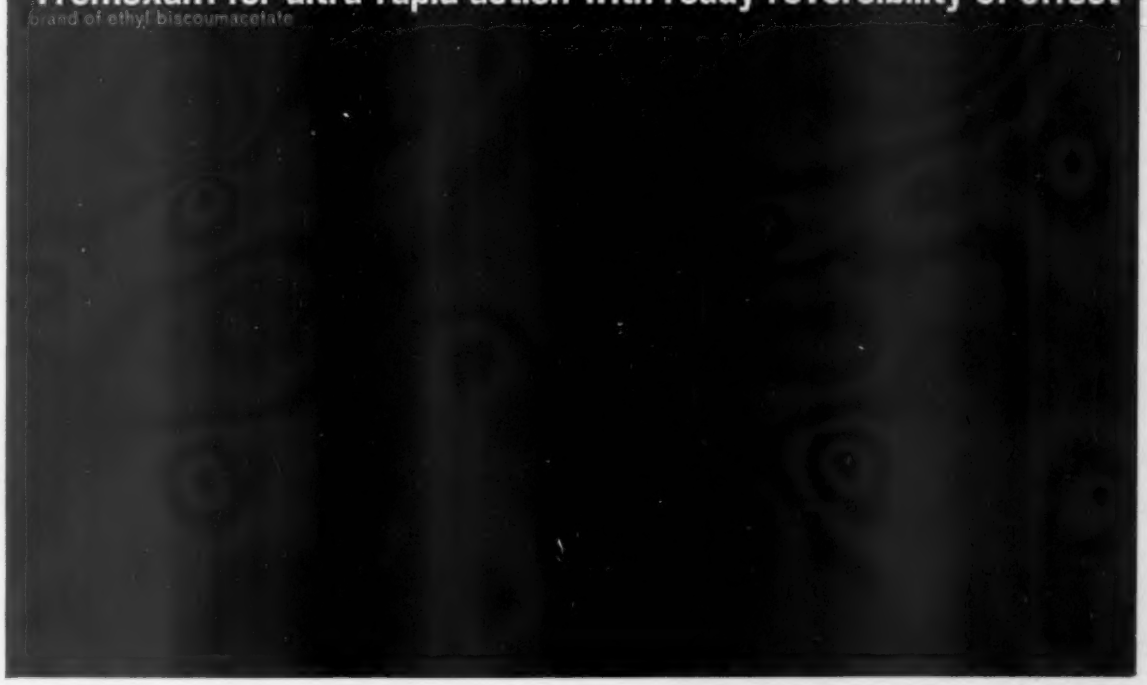

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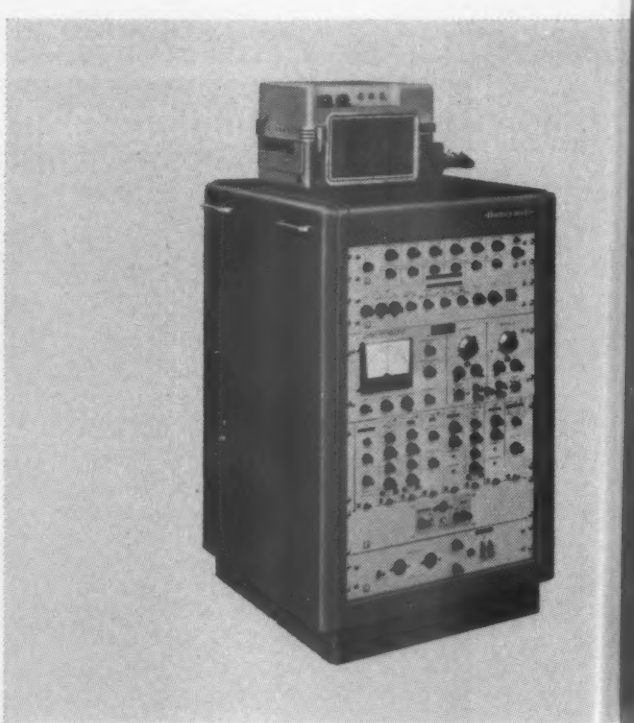

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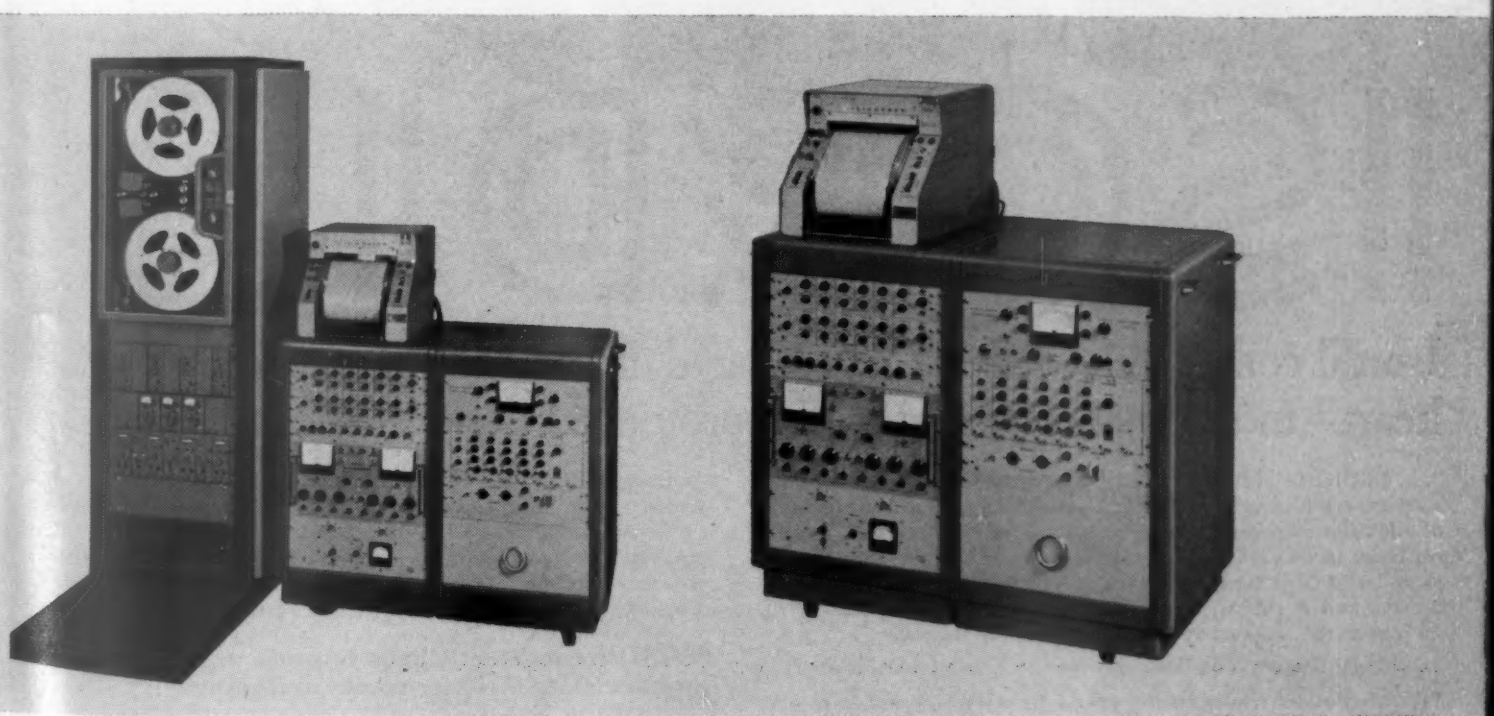

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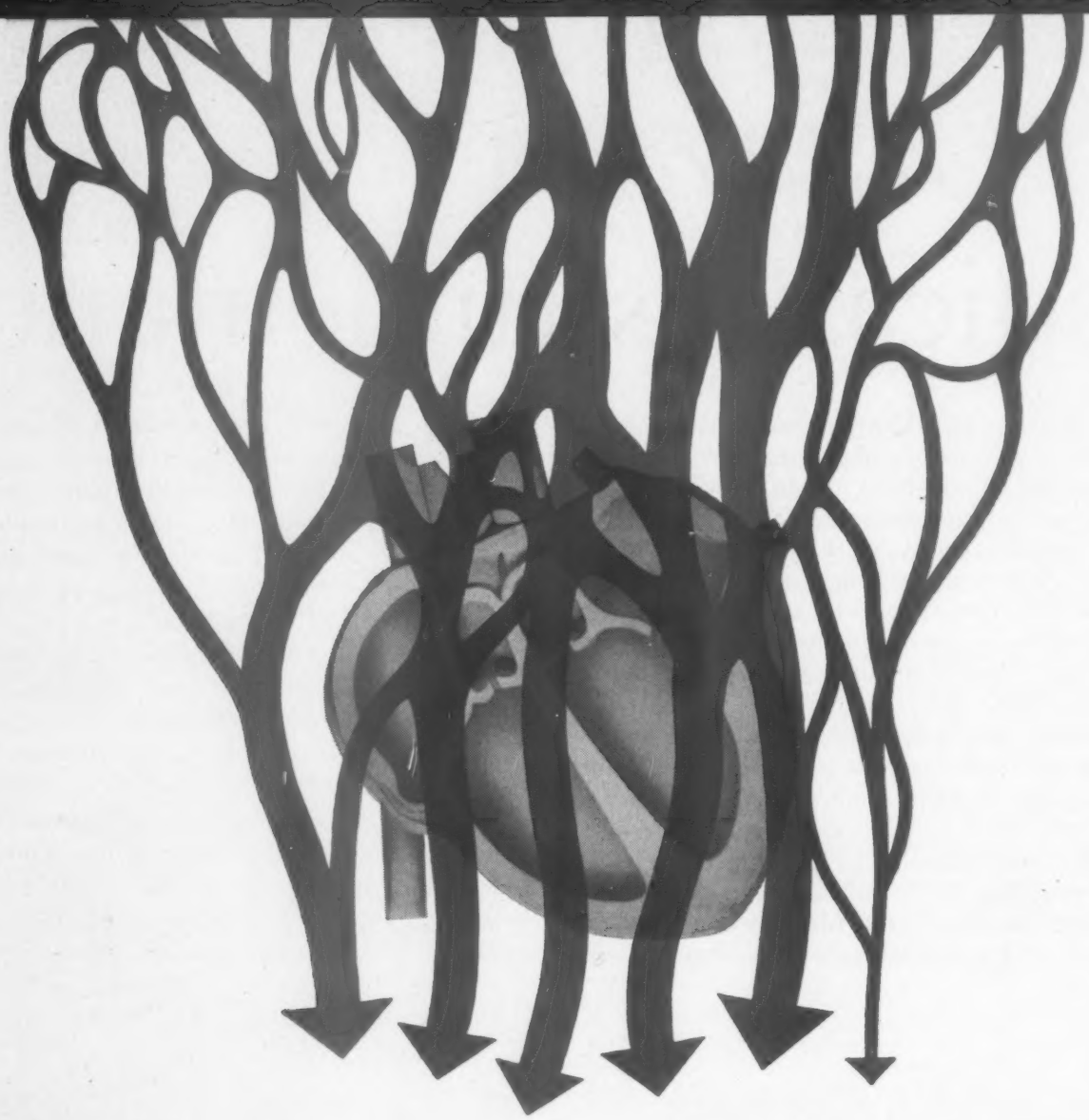

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"If this dosage readjustment would have been possible in the double blind study we might have noted that 85% instead of 65% of all patients would have benefited from isosorbide dinitrate [ISORDIL]."

Fisch, S.; Boyle, A.; Sperber, R.; De Graff, A.C.: A Critical Review of Methods Used In Evaluating So-Called Coronary Vasodilators in Man, paper presented at the American Therapeutic Society Annual Meeting, Miami Beach, Florida, June 10, 1960.

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Albert, A.: Chronic Coronary Insufficiency—Its Treatment with a New Drug (to be published)

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ISORDIL, Isosorbide dinitrate: Effective coronary vasodilator increases flow of blood to heart tissue; reduces frequency, duration and severity of anginal attacks; increases exercise tolerance; decreases pain and reduces (or eliminates) dependency on nitroglycerin. Acts rapidly within 15-30 minutes; benefits persist for at least 4 hours. Side Effects: transitory typical nitrate throbbing; others are insignificant and mild. Dosage: average dose one tablet (10 mg.) q.i.d., a half hour before meals and at bedtime; dosage range 5-30 mg. q.i.d.; individualize dose for optimum therapeutic effect; use with caution in patients having glaucoma. Supplied: white scored tablets in bottles of 100.

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Additional information is available to physicians on request.

1. Selzer, A., and Rytand, D. A.: COUNCIL ON DRUGS, Report to the Council, J.A.M.A. 168:762, (Oct. 11) 1958.

2. Weil, M. H.: J.A.M.A. 171:1868, (Nov. 28) 1959.

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The American Journal of Cardiology

VOLUME VII MARCH 1961 NUMBER 3

Symposium on Rehabilitation in Cardiovascular Disease

Introduction

THE PROBLEMS associated with the rehabilitation of patients with cardiovascular disease will confront the practicing physician and investigator until means are available to either cure or effectively prevent cardiovascular diseases. During recent years an increasing number of publications[1–13] testify to the interest in and the diverse nature of these problems. It is our purpose in this symposium to present the current thinking and practice of some of the leading investigators and practitioners in the field in order to stimulate further interest in these problems, particularly among practicing physicians.

The chief burden of rehabilitating the patient with cardiovascular disease will in the future, as in the past, fall mainly on the patient's personal physician whether he be general practitioner, internist or cardiologist. In order to accomplish his goal the physician will need to consider his patient in a comprehensive manner. Although it is an entirely arbitrary classification, we have found it helpful to break down the rehabilitation process into three phases as follows: (1) the evaluation of the patient and his environment; (2) medical management which should include the prevention or treatment of the underlying disease or its complications, the prevention or treatment of aggravating factors, the regulation of physical activity and the management of psychologic factors; and (3) the re-establishment of the patient in his community. The medical treatment itself will actually be the most standardized and simple of the procedures followed in the majority of patients. The third phase is often the most difficult because either we lack the means of physically or psychologically restoring the patient or the community will not offer him opportunities commensurate with his abilities.

Theoretic concepts of basic physiologic mechanisms in relation to rehabilitation have often been lacking in our concern for more practical problems related to rehabilitation. In his paper in this symposium Jokl has helped to correct this deficiency. He has given us much to think about from the standpoint of the basic physiologic mechanisms related to exercise, fitness and the control of the heart during exercise. He emphasizes here, as he did in his recent book,[14] the importance of nervous system control. In his article regarding the physical rehabilitation of hemiparetic patients Treanor also considers some theoretic points which may have considerable practical application and which may alter radically current methods of rehabilitating victims of stroke.

The importance of properly evaluating and dealing with the psychologic problems is emphasized in the article by Williams and White. This problem has been considered previously in greater detail by Hollender[15] who has also given us better insight into the physician-patient relationship. These problems as they pertain to the patient with cerebral vascular disease are considered by Fisher and he gives us a better understanding of the mechanisms involved in the patient's reaction to his illness as well as useful advice for dealing with these reactions. He considers neurophysiologic and neuropathologic mechanisms as well as psychologic ones in his discussion.

The evaluation of the fitness of a particular subject for physical stress is one of the most difficult aspects of the evaluation of the patient. The fitness test, as described by Levenson and Sparkman, is an effort by a group of skilled

clinicians and investigators to resolve this problem. The test, however, appears to result in a high incidence of T wave changes, S-T depression and ventricular premature beats which suggests that the test needs some further modification before it is widely used. Lacking experience with such a fitness test the practicing physician must obtain the best answers he can by a careful history and an examination of his patient at rest and after exercise of a less standardized sort. Although such assessments of physical fitness are an aid in rehabilitation they do not reveal the patient's ability to adapt to a particular occupational or nonoccupational stress. It is well known that the physiologic load imposed by emotional stress often exceeds that of physical stress in our daily lives and these stresses, as well as those imposed by obesity, diet, smoking and such environmental conditions as temperature and humidity, must be considered in our rehabilitation of the patient with cardiovascular disease.

Many of the physical, psychologic and environmental stress factors are considered in the report on the cardiac farmer by the Purdue group. This is one of the few outstanding studies of its type in cardiac rehabilitation and similar studies should be conducted for other occupational groups.

The results that can be achieved in the vocational rehabilitation of the patient with cardiac disease in industry are described by Greer. The most valuable aspect of his report, however, is the long term follow-up of these patients after they have returned to work. It is only by such carefully conducted studies that we can replace facts for slogans in the rehabilitation of the patient with cardiac disease in industry.

The papers by Master and by Ongley and DuShane on the rehabilitation of patients with coronary artery disease and congenital heart disease, respectively, present the experience of two of the most qualified groups in the field of cardiovascular rehabilitation. Both articles are of interest to the practicing physician.

Two points of view are presented in the articles on the rehabilitation of the patient with cerebral vascular disease. It is refreshing to see the critical approaches to this difficult problem because in spite of the progress of recent years we are all well aware in our daily practice of how much progress must yet be made in the rehabilitation of the patient who has had a stroke.

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Rehabilitation of the Cardiac Patient*

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THERE IS GREAT current interest in cardiac rehabilitation for a number of reasons. With an apparent increase of coronary heart disease in younger men at the height of the most productive period of their lives both physicians and the laity are interested in returning these men to productive lives after the acute episode of disease. In all forms of heart disease there is a steadily improving prognosis with the result that persons with heart disease are able to lead productive lives. Interest in this problem has also been stimulated by the occurrence of major coronary episodes in a number of world leaders. Their return to active and productive lives has dramatically illustrated that people with heart disease can continue to lead active and useful lives. The increasing number of older people, who are particularly susceptible to the ravages of heart disease, is also a cause for great concern to those interested in cardiac rehabilitation.

It is our purpose in this paper to consider some of the following questions:[1,2] (1) what is cardiac rehabilitation, (2) what are the various problems involved in cardiac rehabilitation, and (3) what are the solutions to some of these problems?

Although many definitions of cardiac rehabilitation are available we believe the following is succinct yet comprehensive: A return of the patient to the fullest life possible in every sphere of life within the limits imposed by his heart disease.

PROBLEMS OF CARDIAC REHABILITATION AND SUGGESTED SOLUTIONS

Rehabilitation of the cardiac patient begins on the first encounter of the patient and his physician. We believe that reassurance by the physician that the majority of patients recover from their acute episodes and are able to lead active and productive lives does much to aid the patient in his recovery from the acute episode and serves as a firm basis for future efforts in rehabilitation.

Much effort is needed to re-emphasize the fact that the majority of cardiac patients can be successfully rehabilitated. As recently pointed out by Katz,[3] the medical management of the acute episode is often so exciting and dramatic that the long term problems faced by the patients are often forgotten by the physicians.

The long term problems confronting the patient recovering from an acute cardiac episode touch every facet of life from personal habits to work. These problems are solved most effectively by the patient when he is given detailed advice by his own physician. Some of the problems which may be anticipated are smoking, diet, physical activity, sexual activity and amount and type of work. Detailed advice about all of these problems should be given throughout the convalescent period.

Tobacco: Smoking should certainly be interdicted during acute cardiac illness and later in any patient such as those with angina pectoris, in whom smoking produces symptoms of disease. Some degree of cardiovascular stress is produced by smoking in all patients as evidenced by peripheral vasoconstriction, increase in pulse rate and elevation of blood pressure.

Diet: The period of hospitalization required by an acute cardiac episode offers an ideal time for dietary education and adjustment. The obese patient should have caloric restriction imposed while in the hospital and should be educated in proper eating habits for the future. It would seem reasonable at the present time to put all patients with overt coronary disease on a diet high in unsaturated fat and low in saturated fat.

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Physical Activity: The amount and type of physical activity should be detailed to the patient as convalescence progresses. It is in this area that the most confusion arises when the patient and his family are not given detailed instructions as to exactly what physical limitations are imposed. In the average patient who has had a myocardial infarct a satisfactory plan has been to require three to four weeks of full rest. It should be emphasized that the "arm chair" regimen of Levine does not imply early ambulation but rest in a chair instead of in a bed. In this program the patient is lifted to a bedside chair and is not actually ambulatory. During the next three to four weeks there is gradually increasing activity with a trip or two a day upstairs at the end of this period. Return to work is usually some time during the second to third month. During the latter part of convalescence walking is started (in the absence of complications). The patient walks a block or two at a time at first, increasing the distance every five to seven days until he is walking a mile or two a day.

Sexual Activity: Once the convalescent period is over, sexual intercourse is not to be prohibited in most patients. Those patients who have angina at the time of intercourse may be helped by prophylactic nitroglycerine slipped under the tongue just before beginning the sex act.

Personal and Psychologic Problems: It is as important to educate the patient's family as it is to educate the patient. The rehabilitation efforts of both patient and physician may be greatly hampered by over-restrictive or ill-advised family members.

In a busy hospital environment many of the patient's "worries" which should be considered by the physician are often relegated to the realm of auxiliary personnel such as the social service worker. Social service frequently does an invaluable job in aiding cardiac rehabilitation; however, this job can be done much more effectively if the problems are first considered by the physician and if the solutions have medical sanction.

The personal situation of 223 cardiac patients in a Swedish town (Malmö) of some 200,000 inhabitants has recently been studied by Biörk.[4] This community apparently differs little from many in this country. There has been no great effort at organized rehabilitation or vocational training among the cardiac patients as a group. Biörk revealed that the psychologic problems of the cardiac patient were far more important than the economic and social problems presented by the patient's illness. In a detailed interview with the patients one of the most common complaints was a lack of adequate information about their condition from the responsible physician who frequently "appeared" to have too little time to speak to the patient in detail about the nature of his illness. There was often considerable confusion as to exactly what the patient was allowed to do after he left the protective environment of the hospital. Over-restriction was frequently enforced by the patient's family. Biörk's conclusion of the study is well worth consideration: "As a general conclusion of this study one may be allowed to state that we have found more unsolved problems within the psychological sphere of our cardiac patients than within the economic and social spheres. The psychological difficulties in the course of a chronic illness cannot be easily removed, but if a little more attention were paid to them by the physicians, and if the patients and their families could get a little more information, support, and detailed practical advice, both during the hospital stay and relevant to the discharge home, unnecessary anxiety might be relieved and unnecessary deterioration might be avoided. Physicians should be careful of their own attitudes from the time of the first contact with the patient, in taking the history and making the physical and other examinations, because this first contact will, to a great extent, determine the future interrelationship between the patient and his physician. An optimistic attitude is essential, as already stressed by Sir Thomas Lewis. In dealing with cardiac patients, much may be learned by listening to their heart with a stethoscope, but it may be even more important to listen to the patient himself, without a stethoscope."

Social and Economic Problems: The emphasis on the personal problems of the cardiac patient should not minimize the social and economic problems met by the patient with heart disease. In many of the larger industrial concerns of the country most patients with cardiac disease are taken back after recovery from the acute episode and given full employment. This re-employment is greatly aided by the variety of jobs available within a large industrial concern. However, the problem is much more acute in the small industrial concern and with the cardiac patient who

has been accustomed to doing unskilled manual labor all of his life. Vocational retraining is frequently necessary for these patients. Many excellent programs in vocational retraining for the physically handicapped are offered by most states.

It should be emphasized that the general experience of industry in the employment of persons with cardiac disease has been most satisfactory. Greer,[5] in a recent study of patients with cardiac disease employed at the Gillette Company in Boston, has found the cardiac worker to be actually a little above average in productivity and his absenteeism was only slightly more than the general average. Industry as a whole, however, has been very reluctant to hire a person with known cardiac disease initially because of the fear of a compensation claim should the worker become stricken while on the job. In a study at the Cleveland Work Classification Unit it was noted that cardiac patients have a low rate of absenteeism, work safely and produce well in a wide variety of jobs. It was found that they often improved more than they deteriorated while working.[6] Such studies as these should minimize the "risk" of cardiac employment.

Whenever a patient's work appears to be too taxing a detailed review by the physician of the patient's working day may frequently reveal the source of the difficulty. For example, the patient's work may be well within his capabilities but public transportation may present too great a strain in the form of prolongation of hours or too many subway steps. By spending relatively more on convenient transportation a patient may be able to work when otherwise he might not.

Therapeutic and Preventive Measure: The possibilities of rehabilitation of a patient with cardiac disease have been greatly enhanced by improved methods of treatment of heart disease made available during the past few years. The most dramatic examples of this improved treatment are the patients who have undergone cardiac surgery with subsequent amelioration or complete correction of a cardiovascular defect.

Increasingly effective medical measures are also aiding cardiac rehabilitation. For example, effective oral diuretic therapy enables many patients to be free of edema with a minimally restricted sodium diet. Frequent injections of mercurials are not necessary in many patients. This freedom from injections and from the restrictions of a rigid low sodium diet has increased the capacity for business activities in many patients with cardiac disease. For example, travel, so important in current business, is greatly facilitated.

Prophylactic and preventitive measures are also aiding cardiac rehabilitation. Prophylaxis against recurrent streptococcal infections by the use of penicillin, with subsequent reduction in rheumatic fever, has prevented further cardiac damage in many patients with rheumatic heart disease. Antihypertensive measures have prevented cardiac complications in many patients and have retarded the development of cardiac lesions in others. It remains to be proved whether the various dietary and other measures aimed at lowering the cholesterol levels of the blood will be effective in retarding the ravages of coronary disease. The evidence thus far is at least suggestive that it will be. If effective measures are developed to prevent coronary heart disease one of the most effective measures in cardiac rehabilitation will have been developed.

Summary

A brief review of some of the problems met in the rehabilitation of the patient with cardiac disease with a discussion of some of the possible solutions to these problems is presented. Emphasis is placed on the importance of the physician-patient relationship, on the education of the patient and the public and on the recent advances in therapeutic and preventive medicine which have real or potential value in the rehabilitation of the cardiac patient.

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Cardiovascular Responses to Exercise Concerned in Rehabilitation of Cardiac Patients

Physiologic Considerations*

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IN AN attempt to deal with the subject of rehabilitation of the cardiac patient from the point of view of the physiologist, I propose to discuss two problems: (1) the recent development of Claude Bernard's classical concept of the "milieu interne," and (2) the current revolution in the explanation of cardiac control in exercise.

HOMEOSTASIS AND HETEROSTASIS

In 1867 Claude Bernard pointed out that the body has an exterior as well as an interior environment.[1,2] The latter, he said, is represented by the blood which renders the higher organism virtually independent of its external environment, keeping it "enclosed in a hothouse so that the perpetual changes of the cosmos do not reach it." It was in this connection that he formulated his classical dictum: "La fixité du milieu interne est la condition de la vie libre."

The term homeostasis was introduced by Walter Cannon,[3,4] who restated Bernard's argument and illustrated it with experimental observations of his own:

> "If a state remains steady, it does so because any tendency towards change is automatically met by increased effectiveness of the factor or factors which resist the change. As examples, I may cite thirst when there is need of water; the discharge of adrenalin, which liberates sugar from the liver, when the concentration of sugar in the blood falls below a critical point; and the increased breathing which reduces carbonic acid when the blood tends to shift toward acidity. All these reactions become more intense as the disturbance of homeostasis becomes more pronounced and they all subside quickly when the disturbance is relieved. It is probable that similar corrective reactions appear when other steady states are endangered."

Like all comprehensive monistic theories, Claude Bernard's concept proved to be attractive to medical teachers and investigators. That it contained features of special applicability to the physiology of exercise became apparent first when evidence accumulated to the effect that the autonomic status of highly trained athletes *at rest* differs from that of untrained subjects. The differences under reference also pertain to the cardiovascular system. Athletes' hearts are better capillarized (Fig. 1),[5] their rates are slower,[6] cardiac sizes are greater, stroke volumes smaller, systolic blood pressure is lower (Fig. 2) and diastolic blood pressure higher,[7] "isometric" (more correctly, "isovolumetric") contraction time of systole is longer,[8] pulse wave velocity less rapid, arteriovenous oxygen utilization greater and there are significant differences between trained and untrained subjects in respect to mineral metabolism of skeletal and cardiac muscle tissue. There can be no doubt that *the homeostatic resting state of athletes—not only of their cardiovascular systems—differs significantly from that of untrained subjects.*[9,10]

HETEROSTASIS DURING EXERCISE

Of still greater importance are the physiologic discrepancies which exercise studies of trained and untrained subjects have revealed. During exercise autonomic functions that are homeostatically arranged at rest deploy themselves according to a distribution pattern of their own. In an analysis of acute and sustained high energy output, Fenn[11] has shown that the maximum rate of oxygen consumption in the steady state is about 5.35 L./minute, as against a resting rate of 250 cc., i.e., more than a twenty-one

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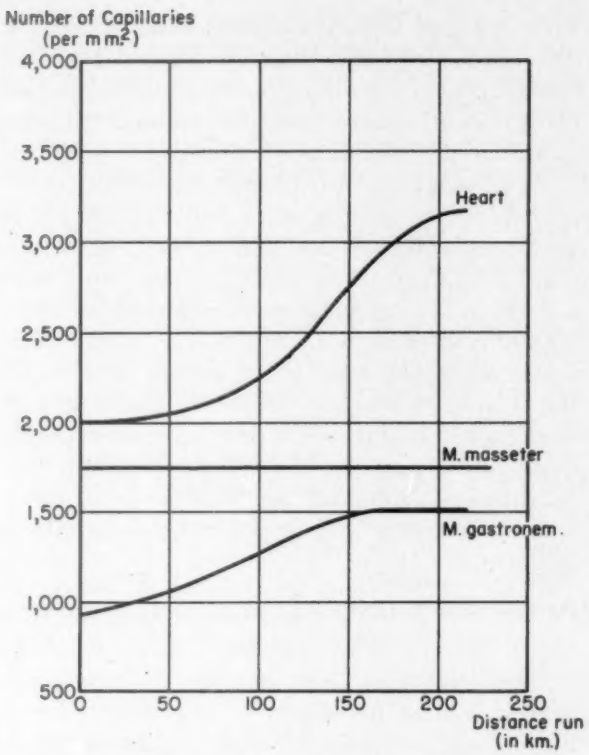

FIG. 1. Capillary density in heart, masseter and gastrocnemius muscles of trained and untrained guinea pigs. (From: PETREN, T. *Verhandl. anatom. Gesellsch.*, pp. 25, 1935.[5])

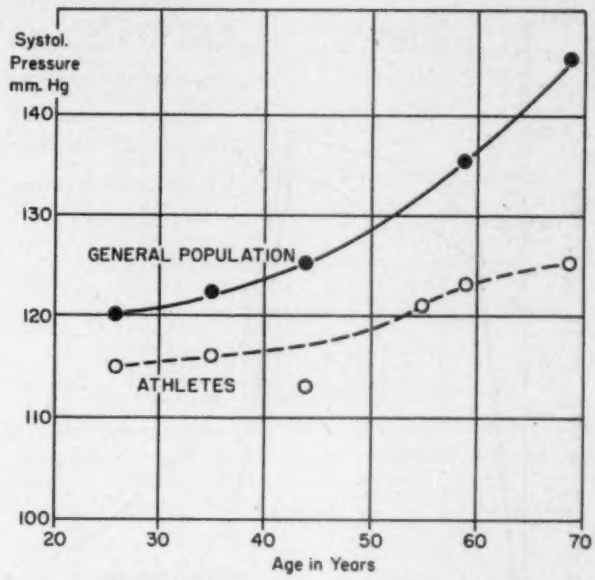

FIG. 2. Systolic blood pressure of trained and untrained men twenty-five to seventy years of age. (From: MELLEROWICZ, H. Vergleichende Untersuchengen über das Ökonomieprinzip in Arbeit und Leistung des trainierten Kreislaufs und sein Bedeutung für die präventive und rehabilitative Medizin. 1956. Steinkopff.[7])

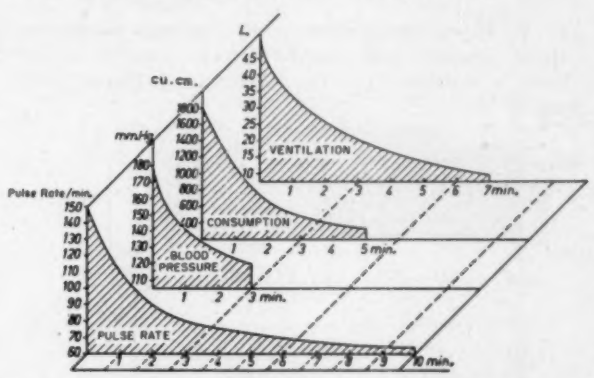

FIG. 3. Recovery period after steady state performance of ten minutes' duration during which a high energy output of 100 watts was maintained. Resumption of *homeostatic* levels of pulse rate, systolic blood pressure, oxygen intake and ventilation is plotted for the four physiologic entities under study. Maximal scale entries on ordinates indicate *heterostatic* activity deployment. (From: HOLLMANN, W. Der Arbeits- und Trainingseinflus auf Kreislauf und Atmung. 1959. Steinkopff.[12])

fold increase. In terms of horsepower this means a rise from 0.12 horsepower to 2.6, or from 90 watts to 1,925 watts. During a one hundred yard sprint oxygen requirements amount to 30 L./minute, corresponding to a release of 14.4 horsepower; but in the approximately ten seconds required for such a race, only about $^1/_2$ L. of oxygen is actually burned in the muscles, so that the runner terminates his sprint with an oxygen debt of 5 L. which is one-third of the maximum oxygen debt possible. Over short periods the body's rate of energy expenditure, or the rate of going into debt for oxygen, might be increased from 250 cc. to 30 L./minute which is about 120 fold. Such figures are but over-all estimates. When an isolated muscle is suddenly stimulated, an energy explosion takes place; and during the actual contraction the rate of initial heat production may be 1,000 times as great as it is at rest.

These data emphasize the magnitude of the autonomic changes during exercise. The principle involved in the functional disengagement under reference is called *heterostasis*. Like homeostasis, heterostasis has a "gestalt" of its own. Primarily, this gestalt is determined by the integrated nature of the discharge pattern of impulses from the central nervous system. A categorical contrast exists between the two functional states under consideration. Nature and extent of this contrast between *homeostatic control at rest* and *heterostatic deployment during exercise* have been demonstrated in studies of recovery of pulse rate, blood pressure, oxygen intake and ventilation after muscular performances in the steady state (Fig. 3).[12,13] Range

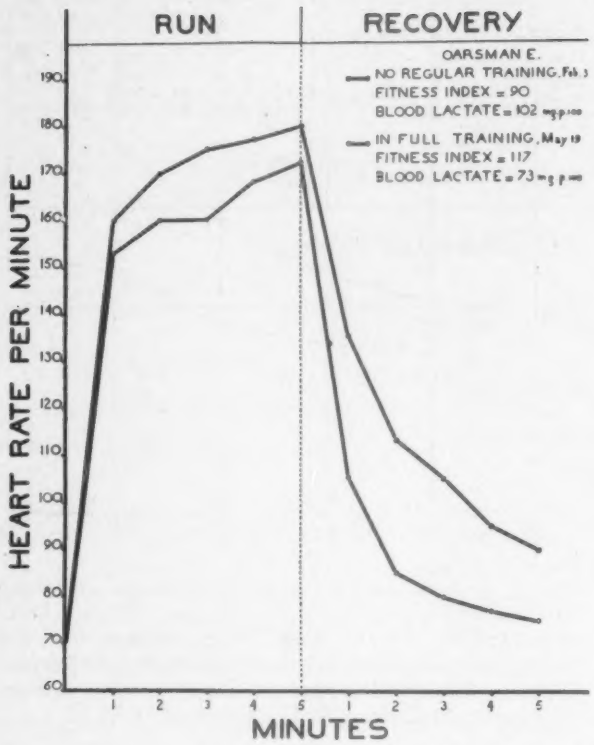

FIG. 4. Heart rate during and after exercise in untrained (upper graph) and trained (lower graph) subjects. (From: BROUHA, L. In: Work and Heart. 1959. Paul B. Hoeber.[6])

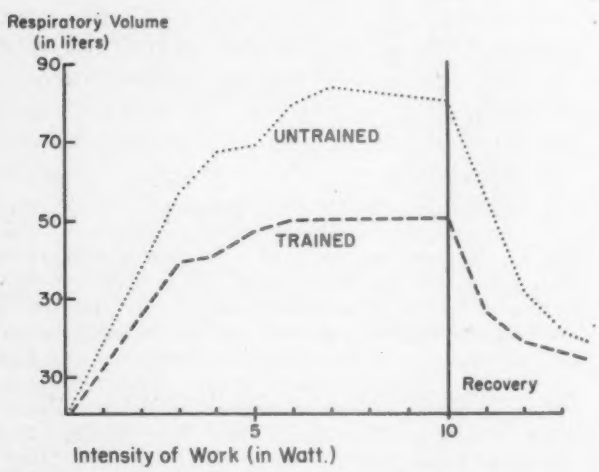

FIG. 5. Respiratory volume during and after exercise in untrained and trained subjects. (From: KNIPPING, H. W., BOLT, W., VALENTIN, H. and VENRATH, H. Untersuchung und Beurteilung des Herzkranken, 2nd ed. 1960. Enke[13]; and HOLLMANN, W. Der Arbeits- und Trainingseinfluss auf Kreislauf und Atmung. 1959. Steinkopff.[12])

and time sequence of the postactivity shift reflect the underlying principle of adaptation which is rendered effective through neurohormonic mediators. Such heterostatic deployment combinations during exercise vary within wide margins during different kinds of activities. However, the data in Figure 3 reflect the temporary nature of the mobilization of the cardiovascular and respiratory resources during muscular performances.

In its original form Claude Bernard's theory related to the resting state only. That it has now been extended so as to include autonomic control during muscular activity represents a development of great physiologic importance. The effectiveness with which the adjustments under reference take place largely determines the degree of success of each neuromotor performance. In Figures 4 to 6 three heterostatic deployment patterns of cardiac, metabolic and biochemical functions are related to different states of training and to the subjects' ability to perform.

AUTONOMIC CHANGES DURING EXERCISE UNDER PATHOLOGIC CONDITIONS

The physiologic juxtaposition of homeostasis at rest and of heterostatic deployment during exercise is relevant for the understanding of many clinical situations. The normal fatigability of the voluntary motor system represents the chief protective mechanism upon which the invulnerability of the heart to athletic effort is based. This invulnerability reflects a biologic law which research on exercise has revealed in its implications for medical cardiology. The autonomic changes which occur during exercise are without pathogenetic significance as far as the normal heart is concerned, because of the briefness of time during which the increased functional demands under analysis are imposed upon it. Even in the most highly trained sportsmen fatigue of the neuromuscular system supervenes long before physiologic limits of the performance capacity of the heart are reached.

The inherent fatigability of skeletal musculature is primarily responsible for the heart's invulnerability against physical exertion. Pulse rates of 150 per minute, systolic blood pressures of 180 mm. Hg, oxygen intake of 1,800 cc. and ventilation levels of 50 L./minute are ubiquitous accompaniments of exercise without evidence of cardiac fatigue, *if performed intermittently*. The self-regulatory time adjustments between rest and activity characterize the physiologic nature of exercise and training.

Under pathologic conditions, however, the myocardium readily develops manifestations of metabolic and mechanical output imbalances

comparable to those that take place under physiologic circumstances in the skeletal musculature during athletic exercise. Under such pathologic circumstances these cardiac imbalances may eventually even become irreversible. But the heart will show manifestations of this nature only if it is exposed *uninterruptedly* or *indefinitely* to the kind of stresses that in the physiologic state make their appearance but *intermittently*, as is apparent from clinical experiences with patients with congenital defects of the heart, arterial hypertension, hyperthyroidism or other endocrine disturbances. In such individuals *permanency of disengagement* of homeostasis is in evidence.

In the light of the facts now known, Claude Bernard's statement has been reformulated as follows: "La fixité du milieu interne est la condition de la vie libre pendant inactivité. La mobilité du milieu interne est la condition de la vie libre pendant travail musculaire."

Cardiac Control in Exercise

Rushmer[14,15] has recently said that a "revolution is currently in progress in the explanation of cardiac control in exercise." This revolution has modified the interpretation of Starling's "Law of the Heart."

In his Linacre Lecture (1918) Starling[16] stated that the mechanisms governing the heart at rest as well as during exercise must be situated in "the walls of the heart itself and presumably in the muscle fibers of which they are composed." Such a view was derived from studies of isolated hearts[17,18] and of the heart-lung preparation which he had perfected. It should be kept in mind that the normal environment of the circulatory system is abolished in such preparations; venous return, intrathoracic pressure, vascular volume, heart rate and arterial resistance are kept constant; neurogenic and humoral influences are eliminated.

Bainbridge[19] attributed the increase of heart rate during exercise to an accelerated "venous return" acting on receptors of the venous and right atrial walls. He drew attention to Krogh's[20] finding that no corresponding change of stroke volume need take place. Subsequently, Heymans'[21] studies of the baroreceptors of the carotid sinus and aortic arch shifted the emphasis upon the role played by changes of the arterial pressure. Exertional tachycardia was thought to be due to a drop in arterial pressure. When it was shown that arterial pressure rises during muscular work, alternative explanations

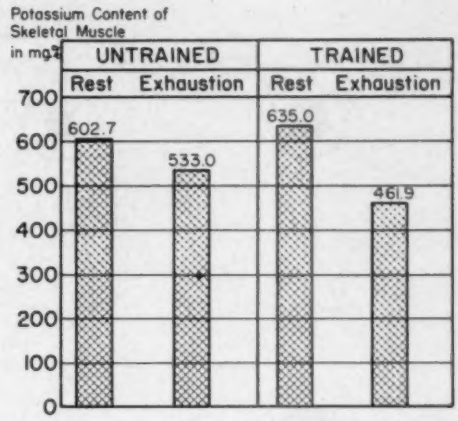

Fig. 6. Potassium content of skeletal muscle during rest and after exhaustive exercise in untrained and trained subjects. (From: Nöcker, J. *Internat. Ztschr. angew. Physiol.*, 17: 243, 1958.[9])

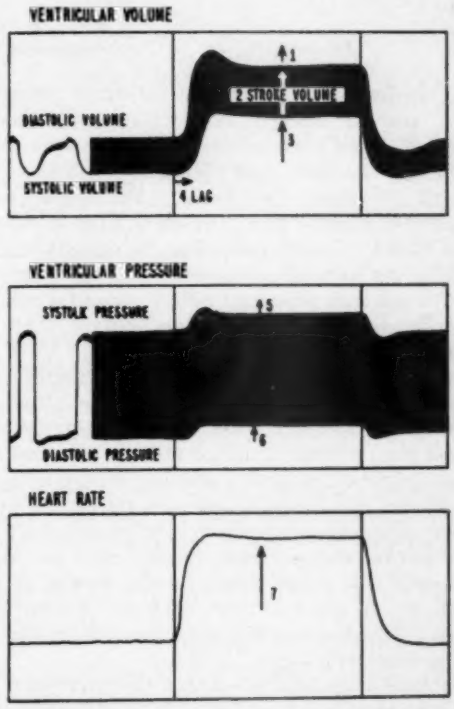

Fig. 7. Classic concept of cardiac adaptation during exercise derived from heart-lung preparation. Diastolic volume (1), stroke volume (2) and systolic volume (3) increase after a lag (4). Systolic ventricular pressure (5), and diastolic filling pressure (6) increase and heart rate (7) rises. (From: Rushmer, R. F. and Smith, O. A., Jr. *Physiol. Rev.*, 39: 41, 1959.[14])

were offered. Today both "local" and "central" control mechanisms of the heart are known to be involved in its response to pressure changes.

According to Starling, cardiac output is augmented by an increase in heart rate. Greater stroke volumes were observed and interpreted as being due to increased "venous return"

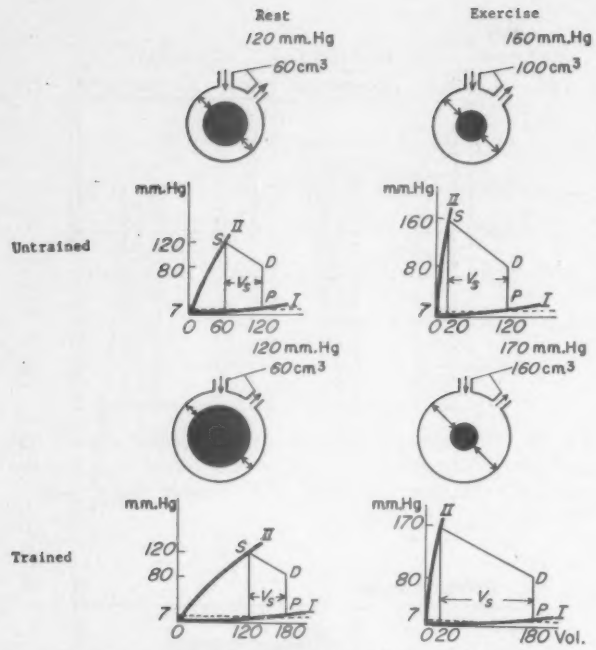

FIG. 8. Performance patterns of the heart of untrained (above) and of trained subjects (below) based on Reindell's[22] didactic use of the pressure-volume diagram of Frank,[17] Straub[18] and Starling.[16] The circular structures represent the heart. Peripheral outlines correspond to cardiac size; the black balls to volume of residual blood. Figures preceding the designation "mm. Hg" refer to arterial pressure; the ones preceding "cm.³" to volumes of venous reflow. I and II are "minima" and "supporting-contraction" curves, these terms being used as in experimental physiology. Vx is stroke volume, P filling pressure, D diastolic and S systolic aortic pressure. All measurements pertain to the left ventricle.

In the upper diagrams, the work of the heart of a healthy adult *untrained* subject is shown at rest (left) and during exercise (right). Systolic arterial pressure increases from 120 mm. Hg at rest to 160 mm. Hg during exercise. Diastolic end volume remains unchanged (120 cm.³) though stroke volume rises during exercise from 60 to 100 cm.³ Residual blood at the height of systole amounts to 60 cm.³ at rest, and to 20 cm.³ during exercise. Pressure volume diagrams reflect the corresponding *dynamic* changes.

In the lower diagram, the work of the heart of a highly *trained* athlete is shown at rest (left) and during exercise (right). Systolic arterial pressure at rest is 120, during exercise 170 mm. Hg. Diastolic end volume of the heart at rest is greater than it is in the untrained: 180 as against 120 cm.³ Stroke volume is 60 cm.³ At the height of systole 120 cm.³ of residual blood are retained in the ventricle. Ratio between stroke volume and residual blood at rest is 1:3, as compared with 1:2 for the heart of the untrained. During exercise the stroke volume of the heart of the athlete increases from 60 to 120 cm.³, as against a corresponding increase from 60 to only 100 cm.³ for the heart of the untrained. In the former, residual blood at the height of systole decreases by an amount of 100 cm.³, viz., from 120 cm.³ at rest to 20 cm.³ during exercise; the corresponding decrease for the heart of the untrained is 40 cm.³. (From: REINDELL, H., MUSSHOFF, K. and KLEPZIG, H. In: Handbuch der Inneren Medizin, vol. 9. 1960.[22])

caused by the pumping action of the active skeletal and respiratory muscles as well as to peripheral vasodilation. Greater venous inflow into the heart was believed to elevate diastolic distention.

In Figure 7 Rushmer[14] has summarized the classic concept of cardiac adaptation during exercise as derived from observations of heart-lung preparations. Diastolic, systolic and stroke volumes are supposed to increase after a lag. Systolic ventricular pressure and effective diastolic filling pressure are believed to do likewise. Heart rate rises.

HEART VOLUME IN UNTRAINED AND TRAINED SUBJECTS

All estimations of stroke volume used until a short time ago were based on indirect evidence. Results were contradictory. It was assumed that the heart of untrained subjects responds to physical exertion primarily by increasing rates without stepping up its stroke volume, while the heart of trained persons utilizes both modalities. A conceptual revolution in applied physiology began when roentgenologic studies in athletes revealed that, contrary to expectation, the diastolic end volume of the heart did not increase during exercise[22–24] (Fig. 8).

Since the early twenties it was believed that the heart responds to an increase of venous return as well as to elevation of arterial pressure by enlargement of its size and by an increase of ventricular filling pressure. In accordance with data obtained in studies with isolated hearts, it was assumed that any enlargement of the human heart denotes an emergency mobilization of myocardial reserves. However, in many pathologic states associated with elevated ventricular filling pressure or increased arterial resistance, the size of the heart does not necessarily change. On the other hand, the heart of the trained athlete, in whom there is no increase in ventricular filling pressure and no elevation of arterial pressure, tends to be larger than that of the untrained[25] (Fig. 9). The concept that the large heart of the athlete represented an instance of myocardial reserves being mobilized and that such mobilization involves a threat of cardiac insufficiency evidently was thus rendered untenable.

The small human heart at rest operates with small amounts of residual blood; the large human heart at rest operates with large amounts of residual blood. These two patterns characterize circulatory situations that are typical

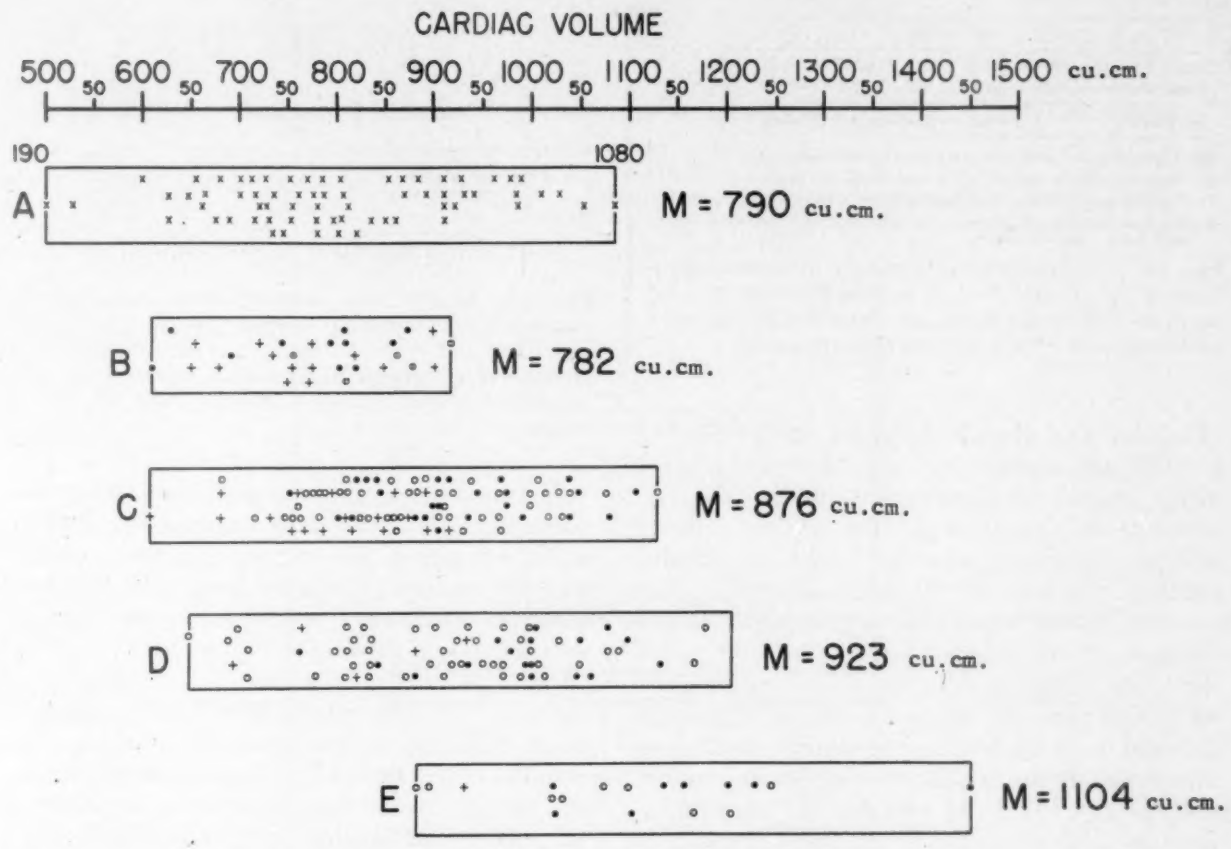
CARDIAC VOLUME
500 50 600 50 700 50 800 50 900 50 1000 50 1100 50 1200 50 1300 50 1400 50 1500 cu.cm.
190
1080
A
M = 790 cu.cm.
B
M = 782 cu.cm.
C
M = 876 cu.cm.
D
M = 923 cu.cm.
E
M = 1104 cu.cm.
Relationship between cardiac volume and physical efficiency.
M = normal hearts.
• = champion athletes
o = ordinary athletes
+ = trained sportsmans of limited performance capacity
A = 67 normal subjects, 20-40 years of age.
B = 30 track and field athletes and gymnasts.
C = 86 middle distance runners, football and tennis players.
D = 66 steeple chase, marathon and other long distance runners; skiers; amateur-cyclists and oarsmen.
E = 18 professional cyclists.

FIG. 9. Effect upon size of the heart of physical activity demanding different degrees of endurance. (From: REINDELL, H., KLEPZIG, H., STEIM, H., MUSSHOFF, K., ROSKAMM, H. and SCHILDGE, E. Kreislaufkrankheiten und Sport. Eine klinische Betrachtung über Leistungssteigerung, Leistungsschwäche und Prophylaxe des Kreislaufs. 1960. Barth.[22])

of the untrained and of the trained subject, respectively. As pointed out before, the heart of the trained athlete is larger than that of the untrained. At the end of systole, the former retains considerable amounts of residual blood while the latter empties itself more completely.[26,27]

ADJUSTMENTS TO EXERCISE IN UNTRAINED AND TRAINED SUBJECTS

The "revolution in the explanation of cardiac control of exercise" of which Rushmer has spoken is still in progress. It is generally admitted that the heart of the trained athlete tends to be larger than that of the untrained; and that the enlargement in question is due to dilatation as well as to hypertrophy. Such myocardial hypertrophy as occurs in athletes is characterized by a conspicuously favorable capillary supply pattern.[28]

At rest the ventricles of the athlete are believed to have forward stroke volumes that are smaller than those leaving the ventricles of the untrained. Considerable amounts of residual blood are retained in the heart of the athlete at the height of systole. The ratio between stroke volume and residual blood is about 1:1 or 1:2 for the heart of the untrained as against a ratio of 1:3 for the heart of the trained (Fig. 8).

During exercise both diastolic and systolic end volumes of the heart decrease. The change under reference forms part of the broad heterostatic shift of the autonomic system during muscular activity, as has been discussed earlier

	MR	ML	Tr	L
Heart diameters 1924	6.0	9.7	15.7	16.2
Heart diameters 1939	4.2	8.8	13.0	13.6
Difference	−1.8	−0.9	−2.7	−2.6

MR—Distance from the midline to the most distant right border.
ML—Distance from the midline to the most distant left border.
Tr—Transverse or maximum broad diameter, obtained by adding MR and ML
L—Maximum long diameter, measured from the right auricular notch to the most distant apical border.

FIG. 10. Orthodiagraphic roentgen measurements of heart of the world champion in bicycle racing (W. R.), taken in 1924 at the height of his career, and in 1939, twelve years after his retirement from the track.[24]

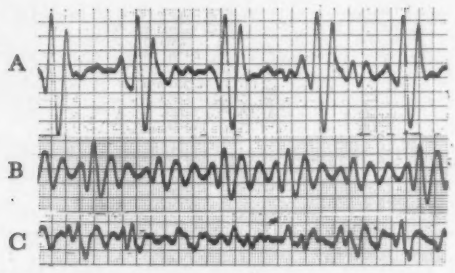

FIG. 11. Direct body contact acceleration ballistocardiograms. A, champion mile runner; B, healthy untrained university student; C, exchampion forty-six years of age (long distance runner) twenty years after discontinuation of training. (From: JOKL, E., *Am. J. Cardiol.*, 4: 105, 1959.[29])

(Fig. 8). End diastolic volumes after prolonged exercise may amount to less than 70 per cent of mean cardiac measurements taken at rest. Systolic end volumes of the athlete's heart during exhaustive exercise yield maximally reduced dimensions. This adjustment is well reflected in the roentgenkymographic pulsation changes of the lateral margins of the heart shadow. Large amplitudes and a sharp apex formation are in evidence during maximal physical activity while exceedingly small amplitudes and blunt pulsation outlines are noticeable at rest. During exercise the amount of residual blood remaining in the ventricle at the height of systole is very much reduced.

Such distinctions in the adjustment of the heart to exercise as exist between trained and untrained subjects are not necessarily demonstrable for every individual couple of corresponding opposites. It is of axiomatic importance to realize that categorical differences from statistical mean patterns of physiologic responses to exercise and training may be encountered in group and in case analyses, respectively. Incidentally, such differences illustrate, as it were, the physiologic principle underlying the integrative action of the nervous system in its projections upon the neuromuscular as well as upon autonomic functions and their adaptive modifications.

That training causes a number of relevant quantitative variants to manifest themselves in the cardiovascular system has been statistically proved over and over; the heart of the untrained responds to exercise with a greater increase in its rate than that of the trained (Fig. 4). The extent of reduction of both diastolic and systolic end volumes of the heart of the untrained is less than it is in the case of the heart of the trained. Corresponding differences are noticeable roentgenkymographically. Tracings from the majority of untrained subjects taken at rest are more sharply delineated while during exercise large amplitudes and sharp apex formation are typical of the athletes' cardiac tracings but are not usually encountered in subjects who are not adapted to the demands of strenuous muscular activity.

To repeat, the morphologic and functional features that are characterstic of the athlete's heart represent a significant *statistical* trend but nothing else. But as Figure 9 shows, the scatter of volumetric measurements taken from hearts of trained and of untrained individuals is such that many an outstanding sportsman can be shown to have a heart smaller than that of many an untrained person. A roentgenogram obtained by us from one of the best long distance runners of the United States showed the heart size so small as to place it near the extreme "left wing" of column A in Figure 9 in which cardiac measurements of untrained young men are plotted. A gradual diminution in cardiac size at rest was found to accompany discontinuation of competitive training in top class athletes (Fig. 10), but individual observations to the contrary are on record. Cureton[28] demonstrated reduction in cardiac size in two middle-aged men after a period of intensive physical training.

BALLISTOCARDIOGRAMS OF ATHLETES

Not so long ago we made the puzzling discovery that exceptionally large, sharply defined amplitudes distinguished the ballistocardiograms of many of the best United States middle and long distance runners at rest[30] (Fig. 11). What about the general assumption today of conspicuously low stroke volumes of athletes' hearts at rest? I do not know. The significance of the above findings was underscored by results obtained in subsequent studies undertaken with highly trained as well as with untrained men and

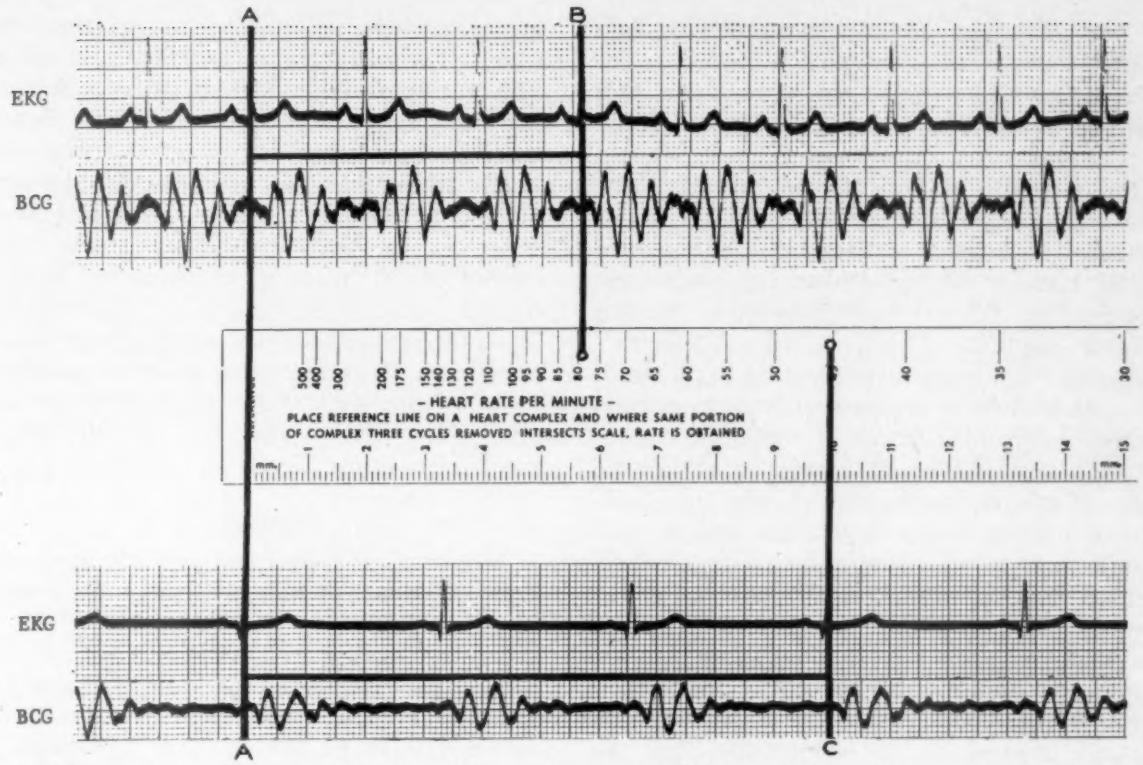

FIG. 12. Top, untrained; bottom, trained. Electrocardiogram (lead I) and ballistocardiogram (direct body contact acceleration recording) of twenty year old student taken at rest before (upper tracing) and after (lower tracing) a seven months' period of intensive training in long distance running. A striking reduction of heart rate (79 to 45) is in evidence. During the seven months there occurred a performance improvement of running times to 10.52.2 minutes from an initial 15.31.4 minutes as measured on the standard cross country course (2.03 miles). The tracings reflect the currently accepted views of the physiologic adjustments to training of the resting heart rates and ballistocardiographic amplitudes, but responses of resting heart rates of this magnitude are rare. Even after the most intensive training of endurance, decreases of more than 25 beats per minute are exceptional. Statistically, bradycardia at rest nevertheless represents one of the most characteristic features of the circulation of champion middle and long distance runners. (From: JOKL, E. In: Cardiology: Vol. V, Related Specialty Fields. 1961. McGraw-Hill.[27])

women who ran two miles on our experimental standard cross country course. Again, some of the findings did not tally with the accepted "rules" of physiologic response to strenuous muscular effort. In fact, cardiac work output at rest as assessed from IJ amplitude analyses in the ballistocardiogram is significantly greater in trained than in untrained subjects, as well as in "good" and "bad" long distance runners with running times being taken as criteria of performance rating. In some of the best runners we found low postexercise amplitudes in the ballistocardiogram while some of the least efficient runners showed very high deflections immediately after the race. In other words, the statistical pattern (Fig. 12) need not be reflected in every case at all. Stroke volume responses to athletic exercise as well as to training are evidently controlled according to a more complex regulation pattern than is generally assumed at present. Recent studies have shown that all these adjustment mechanisms to exercise have long term implications in respect to cardiovascular morbidity and mortality patterns.[31,32] The whole problem required further studies.

PHYSICAL FITNESS IN HEALTH AND DISEASE

Numerous clinical case reports of subjects with high athletic efficiency in the presence of cardiac abnormalities leave no doubt that cardiac stroke volume is one of several determinants of physical endurance, but certainly not the only one. The role played by adjustments of stroke volume for physical endurance may be modified by other heterostatic influences some of which are evidently not yet fully understood. It is only with such an assumption that one can explain why athletes with complete atrioventricular block, with aortic regurgitation and mitral stenosis, with interatrial or interventricular septal defects, with block even of large branches of the coronary artery, have been able to participate successfully in athletics. At the same time the need for prolonged bed

rest has remained an important medical rule adopted daily in cardiological wards. An attempt must be made to disentangle this puzzling complex of seemingly irreconcilable observations. My impression is that physical fitness in health and in disease depends more than has hitherto been realized upon nervous control, and that the categorical significance of the stability of the underlying pathologic processes has not yet been sufficiently stressed in this context. I agree with Rushmer's view that "the integrative function of the nervous system must be a primary factor in normal cardiac control," though I have no doubt that the same statement applies to pathologic states of the cardiovascular system. By integration I mean in this respect the flexible combination of functional units in varying arrangements; that is, a physiologic state of affairs corresponding to that which was clarified one hundred years ago by Hughlings Jackson when he studied the role played by the cerebral cortex in the control of voluntary movements. Jackson arrived at the conclusion that the cortex is concerned with the attainment of motor aims and not with the activation of fixed muscular contraction patterns. The similarity between the two instances, the one taken from circulatory physiology, the other from neurophysiology, is by no means simply allegorical. After all, the cardiovascular system is the chief autonomic supporting agency for the execution of the neuromotor system's tasks. In the process of satisfying the body's oxygen needs as well as its thermoregulatory requirements during exercise, the cardiovascular system is in a position to use different partial functions in varying combinations at different times, under the same or under different circumstances. Nervous impulses mediated by cortical, subcortical and midbrain levels play a decisive role in "steering" cardiovascular adjustments to the demands of muscular activity in an appropriate manner.

Permanent or chronic adjustments of autonomic functions to training frequently represent secondary events in accordance with the hierarchic scale to which integrative physiology is bound. It is insufficiently known that the physiologic adjustments under reference follow and do not precede the establishment of the individual's improved neuromotor performance capacity. The latter is, of course, the chief indicator of the efficacy of the training process. During 1959 we conducted an intensive physical training experiment with university professors who were between thirty-five and fifty years of age. The latter participated for six weeks in an intensive daily exercise program consisting of calisthenics, apparatus gymnastics, swimming, weight lifting and play activities. A highly significant performance improvement was in evidence at the end of the six weeks. Such cardiovascular training adjustments as could be demonstrated were slight and quantitatively incommensurate with the neuromotor achievement gain. No effect whatsoever had established itself at the same time in respect to blood cholesterol levels and to the coagulation mechanism of the blood.

Summary

This paper is concerned with two key physiologic problems upon which the understanding of rehabilitation in cardiology rests: (1) The recent elaboration of Claude Bernard's classical idea of the "milieu interne" and (2) the current revolution in the explanation of cardiac control in exercise in physiologic and pathologic circumstances.

As to the first, the concept of homeostasis has only recently come into its own because of the clarification of the juxtaposition of the homeostatic situation *vis-a-vis* the diametrically different pattern of disengagement of the autonomic components which are encompassed by both. The disengagement from the homeostatic resting state—originally identified during physiologic analyses of exercise situations—is called heterostasis. As a result of the understanding of the bipolar nature of the relationship between homeo- and heterostasis a new and fruitful approach has evolved in respect to the diagnostic and prognostic assessment of the cardiovascular system's actual and—in view of our growing knowledge of the training process—also of its potential resources. In athletics as well as in clinical medicine new vistas have thus been unfolded and the quantitative determination at rest and during exercise of circulatory functions such as heart rate, blood pressure, stroke and minute volume, oxygen intake and ionic exchanges has thereupon assumed a new importance.

Secondly, in order to grasp the full implication of the issue in situations with which the physician is confronted when considering the appropriateness of applying physical training in the restorative treatment of cardiac patients another question must be considered: that of the

stability of the underlying pathologic process. The answer to this question determines from case to case whether exercise and training can be applied in the treatment of cardiac patients or, in other words, whether their condition is amenable to active rehabilitative treatment.

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Exercise Testing of Cardiac Patients in Evaluating Work Potential*

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IT HAS BEEN WELL demonstrated that the person with heart disease can be an effective and productive worker if placed on a suitable job. The work of Goldwater[1] and Hellerstein and Goldston[2] among others has demonstrated this fact in a convincing fashion. The work records of patients who have been studied by the various cardiac work evaluation clinics have been impressive, as has the number of cardiac patients who were judged able to return to work.[3] Finally, there is no substantial evidence that appropriate work has had any adverse effect on the course of the workers' heart disease.[4]

In advising cardiac patients about activity it is essential to know as precisely as possible the patient's functional capacity. Recommendations for training, change of job or continuing the same work hinge on the patient's tolerance to exercise. In clinical practice the determination of functional capacity is based on the patient's history and is not subject to any means of confirmation. Reports in the literature[5,6] suggest that this means of determination may not be entirely accurate or satisfactory. The increasing acceptance of cardiac workers by industry makes accuracy a matter of practical significance to the patient and to industry.

Exercise testing has been advocated to aid the evaluation of cardiac patients. Warren,[5] in reviewing the subject in 1952, recognized that there were deficiencies in clinical evaluations. He discussed the various test procedures recommended and concluded that they contributed little to the clinical evaluation. He expressed the hope that a suitable test of functional capacity might be developed. Harris[7] felt that the parameters of the tests that had been devised had too many variables to be reliable.

Objections have been raised to exercise for cardiac patients on the grounds that it is dangerous, unnecessary and adds little useful information. There are a few case reports of the adverse effects of exercise usually occurring during an anoxemia or Master two-step test.[8] Such tests are usually performed as diagnostic procedures to aid in the evaluation of pain in the chest and not for the purpose of determining functional capacity.[9]

Bruce[10] has reported extensively on the value, safety and reproducibility of an exercise test using a motor-driven treadmill, the physical fitness index. He and other investigators have used this test for a variety of clinical and investigative purposes. It is the purpose of this report to present data and impressions obtained by the use of Bruce's exercise test on a group of cardiac patients who were evaluated at the Washington Cardiac Work Evaluation Clinic for return to work.

PROCEDURES

All patients had a medical history and physical examination by a staff physician, a roentgenogram of the chest, fluoroscopy, electrocardiogram, timed vital capacity and routine blood and urine examinations. The functional and therapeutic status was estimated according to the classification of New York Heart Association.[11] Patients were also interviewed by a psychiatrist, a medical social worker and a vocational counsellor. After these interviews and examinations were completed the exercise test was performed.

The test used, the physical fitness index, has been described by Bruce et al.[10,12] The test required the patient to walk on a motor-driven treadmill traveling at 150 feet per minute on a 10 per cent grade for ten minutes or until he was forced to stop by symptoms. The blood pressure, electrocardiogram† and respira-

† A tracing was obtained by attaching the left arm lead to a chest electrode at the V_5 position, the right arm lead to an electrode near the tip of the right scapula, and the right leg lead to a right chest electrode. The tracing is recorded from the lead I position on the electrocardiograph.

* From the Washington Cardiac Work Evaluation Clinic, Seattle, Washington.

TABLE I
Classification of Patients by Diagnosis

Diagnosis	Per cent of Patients
Coronary arteriosclerosis	68.2
Hypertensive cardiovascular disease	2.2
Rheumatic heart disease	16.0
Congenital heart disease	4.0
No heart disease	7.0
Undiagnosed manifestations	2.6

tory efficiency* were recorded at each minute of the test.

Prior to exercise these data were recorded for four minutes with the patient sitting and for one minute standing. After the exercise was terminated the same information was recorded for five minutes. These intervals were the same whether or not the patient was able to complete the prescribed ten minute exercise period. The patient was questioned about any symptoms which may have developed and was examined to determine the presence of any cardiopulmonary abnormalities which may have occurred. Positive findings were recorded.

A score, the *physical fitness index*, was derived from the data obtained according to the following formula:

$$PFI = \frac{E \times R \times K}{C}$$

E = duration of exercise in minutes; R = average respiratory efficiency during exertion; K = 100, a constant; C = cumulative heart rate for the first three minutes of recovery.

Normal values for this test range from 13 to 26; there is a high degree of reproducibility.

RESULTS

Three hundred and sixty-six patients of the Washington Cardiac Work Evaluation Clinic were referred for exercise testing. For various reasons 4 per cent of the patients were not exercised. Only four persons were rejected from testing because of the severity of their heart disease. All of these four had symptoms of recent origin suggesting impending myocardial infarction. Most of the tests have been performed by one examiner.

Table I classifies the patients by diagnosis. As might be anticipated, the majority of patients had arteriosclerosis with a moderate number having some form of rheumatic valvular disease.

* By means of a face mask and tubing the expired air is pumped through an oxygen analyzer. The difference between the oxygen content of the inspired and expired air is termed the respiratory efficiency.

TABLE II
Symptoms During Exercise Testing

Symptom	Per cent of Patients
Dyspnea	54
Fatigue and weakness	36
Chest pain	26

RESULTS OF EXERCISE TEST

Symptoms During Test: Of the 351 patients actually tested 65 per cent were able to complete the prescribed ten minute walk, 15 per cent were able to walk three to nine minutes and 20 per cent were able to walk three minutes or less. Tests were most commonly terminated because of the development of dyspnea, fatigue or pain in the chest. These symptoms developed in milder degree rather often during the test (Table II) but did not always require termination of the test.

Dyspnea was the most frequent complaint, occurring in 54 per cent of the patients. It was moderate to severe in 44 per cent of the patients. Chest pain of moderate to severe degree developed in 33 per cent of the patients with coronary atherosclerosis.

Regardless of the severity of the symptoms, most had subsided by the end of the five minute recovery period. An occasional patient complained of fatigue and vague chest discomfort that continued for several hours. Re-examination of these subjects has failed to reveal evidence of worsening of their heart disease.

Electrocardiographic Changes: These were seen in 25 per cent of the patients (Table III).

TABLE III
Electrocardiographic Changes

Change	Per cent of Patients	
	During Exercise	During Recovery
S-T segment depression	21	16
T wave changes	24	18
Premature ventricular contractions	14	2

In general these changes appeared in the patients with the symptoms previously described. It was our policy to continue the test in the presence of electrocardiographic abnormalities unless symptoms appeared. In patients receiving digitalis it was not uncommon to find significant S-T segment depression without the appearance of symptoms. Rheumatic patients without evidence of coronary artery disease occasionally exhibited this finding.

Various types of T wave changes including inversions, lowering and increase in height, have been observed. In some instances significant S-T segment changes appeared during exercise, disappeared promptly with rest and were replaced by striking T wave changes.

Premature ventricular contractions during exercise developed in 14 per cent of the patients. Such changes have been regarded as evidence of myocardial irritability when they were observed during or after exercise.

With one exception all of the changes during testing had returned to normal by the end of the recovery period. Left bundle branch block developed in one man during exercise and has persisted.

CORRELATION WITH CLINICAL CLASSIFICATION

After the testing and interviews were completed, the material was presented at a team conference. At this time a comparison was made between the functional classification as determined by the clinician, and the exercise performance in terms of score, duration of exercise and symptoms. If the exercise performance was consistent with the clinical estimation of functional capacity the latter was accepted. If there was an obvious discrepancy between the functional capacity and the exercise performance, both the test result and the clinical estimate were reconsidered; only then was the clinical classification made final.

In 75 per cent of the cases, the patient's exercise performance and his clinical classification were in accord. However, in 20 per cent of the tests the clinical estimate and exercise performance seemed clearly inconsistent. On review of both, the clinical evaluation was usually found to be in error. Taking the history again or reconsideration of the original history resulted in a change of functional classification in this group. The classification was raised in 11 per cent and lowered in 9 per cent of the patients.

TABLE IV
Factors Responsible for Errors in Clinical Evaluation of Functional Capacity

Factor	Per cent of Patients
Inadequate history	13.0
Patient's tolerance too limited to test	4.0
Other diseases more limiting	2.5
Recent recovery from illness	0.5

Factors Causing Errors in Clinical Evaluation: A number of factors were responsible for the errors in the clinical evaluation of functional capacity (Table IV). As indicated, the primary reason for error appeared to be an inadequate history. Some patients were unable to give a history that permitted an accurate determination of functional capacity. In others there was faulty interpretation of the history. Many of the patients were not able to describe their activities in terms that had meaning to the examiner. For example, a farmer with cardiac disease complained of severe symptoms with what he and the physician considered to be a routine work load and he was classified in class IIC. However, he was able to complete the full exercise test without symptoms or electrocardiographic changes and had a normal test score. In retrospect his work was exceedingly strenuous, requiring much more effort than the examiner had been led to believe.

A significant number of patients had limited themselves to such a degree that any attempt at classification without some form of an exercise test was little more than an educated guess. Frequently, patients of this group limited themselves because of noncardiac symptoms (pain in the chest wall, dyspnea due to pulmonary disease) which they considered to be of cardiac origin. Because of the fears associated with these symptoms they were reluctant to exert.

On occasion the family, friends and even the physician being fearful that "work causes heart trouble" restricted the patient well beyond the time that is considered necessary by the current concepts of heart disease. As with the group previously described, these patients had not had an opportunity to learn their limits.

The patients who were tested soon after recovering from an illness such as a myocardial infarction had not had an opportunity to learn

whether any limitations had been imposed by the disease.

DRAWBACKS AND VALUES OF TEST

The test was not infallible. On a few occasions the patients exhibited so much anxiety at the prospect of being subjected to exercise that they were unable to perform adequately. A few were very distressed because of the face mask and could not perform satisfactorily. The test was of limited value in some of the patients with heart disease who also suffered from some other disorder such as cerebrovascular disease, emphysema and peripheral arteriosclerosis. However, even in these patients there was often value in determining both the nature and degree of disability under direct observation. It has been the policy of the clinic to exercise all of the patients other than those previously described as exempt and those with complaints of acute cardiac disease. With these exceptions the test has been a valid and satisfactory indication of the patients' functional capacity.

In addition to the data provided on functional capacity, the test had an unexpected therapeutic value. Some of the patients who had been fearful and had restricted themselves needlessly gained confidence by exercising in the presence of a physician and while attached to an electrocardiograph and other monitoring equipment. This new confidence frequently seemed to be an important part of a successful return to employment. The converse was also noted. A patient who denied his symptoms was able to accept his limitations and to adjust to these limits. These observations frequently have been volunteered by the patients on follow-up visits. Although they were purely subjective, these factors were important in motivating some patients to return to work.

COMMENTS

In a discussion of exercise tests, the use of other tests, particularly those which may be applicable to office practice, should be considered. Although a treadmill is available for office use, few practitioners are likely to obtain one. A modification of the treadmill test has been described[13] using a step and measuring essentially the same parameter as the physical fitness index. It has proved a satisfactory procedure for office use.[14]

Although a Master two-step test is commonly used as a method of confirming the presence of coronary insufficiency the physician may obtain valuable data on the individual subjects functional capacity by observing the performance of the test.[15] This test requires a greater expenditure of energy in a shorter period of time than does the physical fitness index. The energy costs may be greater than that of many jobs as well. Ford and Hellerstein[16] have studied and reported on energy demands of this test and related these demands to those of various types of work.

Should the examiner wish a less elaborate evaluation, he may observe the patient in the performance of some simple exercise. Observing the manner in which a person climbs a flight of steps may provide much information. Attention should be paid to the speed with which he walks, the character of his respirations and whether he complains of symptoms with this degree of exercise. The patient who has symptoms after climbing one or two flights of steps, especially at a slow rate, is moderately disabled (functional class II and III).

SUMMARY

Recognition has been given to the fact that in some instances a clinical evaluation may not be a suitable means of determining the functional capacity of a cardiac patient. The proper determination of this status is of great importance in advising a patient as to what activity and work he may safely undertake.

An exercise test has been used as a routine part of the evaluation of patients seen at the Washington Cardiac Work Evaluation Clinic.

Seventy-five per cent of the patients performed the test in keeping with the clinical estimate of their disability. In 20 per cent the patient's functional classification was changed at least one grade when he was re-evaluated after being tested. The reason for such variations may not be obvious to the examiner without the information provided by an exercise test.

Although symptoms of disease and electrocardiographic changes were commonly noted in patients taking the test, all had subsided by the end of the recovery period except for a persisting left bundle branch block in one case.

Many of the patients have reported increased confidence in their ability to exercise safely after the test. Others are finally willing to accept their limitations.

Simpler forms of exercise test are readily available to most clinicians. Use of such

tests could provide the physician with sounder basis for advising his cardiac patients.

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Rehabilitation of the Child with Congenital Heart Disease*

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More than 35,000 children with congenital heart disease are born in the United States each year. Depending on the seriousness of their illness and the attitudes of those persons caring for them, these children may have relatively pleasant or extremely difficult lives.

In this paper we shall stress particularly those aspects of rehabilitation which will enable the child with congenital heart disease to become an integral member of his family and community and to attain his maximal physical, emotional and scholastic development.

THE GOALS AND HOW TO ACHIEVE THEM

In our efforts to assist the handicapped child we must formulate goals which are reasonable and realistic. The majority of patients with congenital heart disease will be able to live and work in an essentially normal and productive manner. Some, because of other congenital deformities or because of the seriousness of their disease or its complications, will be more limited and their life span also may be diminished. The program outlined for each child must be individualized and based on a realistic assessment of the severity of the disease and the ultimate attainable social status of the child. We must assist each child to reach the fullest measure of intellectual, social and emotional development of which he is capable. The more complete the emotional and intellectual development, the better able is the child to accept his physical disability and compete with his peers. Undue restriction or overindulgence because of physical disability tends to divorce the child from the realities of everyday life and to make him less well prepared to cope with problems in the future.

Medical Evaluation: Complete medical evaluation of each patient is essential. An accurate diagnosis and a thorough knowledge of the natural history of the disease process allow proper treatment to be outlined and the prognosis to be determined. Without the basic items of diagnosis, treatment and prognosis it is not possible to establish an intelligent and comprehensive rehabilitation program. Exact diagnosis and prognosis are not always possible in infancy and in some cases a final opinion must be reserved until further observations or the performance of more complex diagnostic studies clarify the situation. Even without an exact diagnosis the problems should be explained to the parents as clearly as possible. This requires time but is essential and the time is well spent.

Personnel Who Must Cooperate: Many persons are involved in the rehabilitation of a child with congenital heart disease. These include the patient and his immediate family, the doctor, the social worker, the child's friends and teachers and, later on, his employers. All must try to understand the handicaps of the child but all must work toward making him as nearly a normal member of the community as is possible. This requires time, effort and sacrifice on the part of everyone involved but these are a small price to pay considering the dividends that result.

The cooperation or otherwise of a patient's family can help or obstruct rehabilitation. Sympathy and understanding with a clear conception of the objectives of treatment can help tremendously. Resentment, indifference, overprotection or ignorance may delay or permanently obstruct successful rehabilitation.

The family physician is of great importance. He is the person who makes the original diagnosis of heart disease; he selects the institution to which the patient will be referred; he is

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acquainted with the parents and the rest of the family and knows the community and the environment in which the child must live. He has knowledge of local educational and welfare agencies which may be utilized to the child's advantage and he provides a continuing source of moral support and medical advice to the patient and his family.

Classification

For the purposes of our discussion children with congenital heart disease may be placed in the following groups: (1) those with surgically correctable lesions resulting in a normal circulatory system; (2) those who can be only partially helped by operation or who have postoperative heart block; (3) those for whom nothing can be done surgically but can be helped medically, and (4) those for whom no satisfactory medical or surgical treatment is available.

Age for Corrective Operation

The ideal age for corrective surgery is that at which the operative repair can be done with a minimum of risk, and the child's physical and mental status will receive the maximal benefit. The ideal time for operation will vary depending on the nature of the underlying lesion. For intracardiac operations using extracorporeal circulation the technical difficulties are much less in children who are more than two years of age than in those who are less than one year old. Most operations are best performed before a child starts school; he then can start off on even terms with his peers. In certain instances of large patent ductus arteriosus or severe valvular pulmonic stenosis, the risk of delay may be such that corrective operation is desirable during the first few months of life. With other lesions, such as coarctation of the aorta, it may be considered desirable to postpone the operation until the child is ten to twelve years of age.

Surgically Correctable Congenital Lesions

Patients with this type of disorder may have one of several lesions, such as patent ductus arteriosus, coarctation of the aorta, ventricular septal defect, atrial septal defect, pulmonic stenosis and sometimes aortic stenosis. Each of these lesions is completely correctable when uncomplicated and the child then can be treated as a perfectly normal person. Physical restrictions usually are suggested for a few weeks to a few months after operation depending on the age of the child. There is no point in trying to restrict the exercise of a small baby with a patent ductus arteriosus but the activities of a ten to twelve year old child who has had a recent repair of a ventricular septal defect or of aortic stenosis should be restricted to a moderate degree for the first one to two months after operation. The activity should be gradually increased and full activity may be resumed by the end of three to four months.

General Rules: For this group of patients with operable and correctable lesions a few general rules should be made.

1. Any child who has had congestive heart failure before operation is probably best maintained on a diet low in sodium and should receive digitalis for four to six weeks after operation, although a few are improved so dramatically that no medication is necessary.
2. Patients having congestive heart failure after operation should be maintained on a diet low in sodium and should receive digitalis and other anticongestive measures such as diuretics for as long as is necessary. This period is usually four to six weeks but may be six months or more.
3. Restriction of exercise is impossible for a small baby; it is difficult for children two to five years old but is well worth while for children ten to fourteen years old because participation in competitive athletics is part of the normal life of this group.
4. Overanxious parents must be reassured time and again that their child is cured because it is difficult for them to change from an overprotective attitude to the realization that their child should be considered normal.

Congenital Heart Lesions Partially Correctable by Operation

Some forms of congenital heart disease with severe or multiple defects may be only partially correctable surgically. Examples are as follows: (1) partial or complete atrioventricular canals in which the intracardiac shunts may be repaired, but varying degrees of mitral insufficiency may persist; (2) left-to-right shunts with moderate to severe pulmonary vascular obstruction which persists after closure of the shunt; and (3) development of complete heart block after repair of a cardiac lesion. In these patients, operation has been only partially successful and the severity of the residual lesion will determine the degree of circulatory embarrassment.

If the residual disability is severe, medical treatment must be directed toward improving the cardiac status; long-term treatment, including vocational guidance and physical activity, must be planned with due consideration of the patient's limited abilities. If a patient has severe mitral insufficiency he probably will require prolonged anticongestive therapy but he may do well after several months and is not likely to die suddenly without a prolonged period of congestive heart failure. By contrast, the patient with severe pulmonary vascular obstruction may seem to do well after operation and may require only a short course of supportive therapy but he may die suddenly at any time, days, weeks or months after operation. Patients with pulmonary vascular obstruction of a lesser degree have not been followed long enough after closure of left-to-right shunts for an accurate long term prognosis to be determined.

Complete Heart Block After Intracardiac Surgery: The rehabilitation of patients with complete heart block following cardiac surgery can involve a tremendous emotional strain for both the patient and the entire family. Unlike patients with congenital complete heart block who are usually asymptomatic, patients with postoperative complete heart block may have attacks of dizziness or fainting; sudden death may result. Of twelve patients discharged from our institution with this complication during the past few years three have died, three have severe symptoms of dizziness and fainting and six are asymptomatic with limited activity. Careful observation of the symptomatic patient places tremendous tension on a household. Mothers do not dare to leave their children for even an hour or two without someone conversant with the problem keeping a careful vigil. Some children who have progressive bradycardia before they become symptomatic may be able to take sublingual isoproterenol hydrochloride (Isuprel®) and abort the attack, whereas others may have a sudden period of asystole with the rapid onset of unconsciousness. To rehabilitate these children to anything approaching a normal life is almost impossible. At best, one can try to adjust the dosage and frequency of administration of isoproterenol to keep the patient as free from attacks as possible. For the rest it is hoped that with the passage of time the attacks will become progressively less frequent and will ultimately disappear. Unfortunately, this is not always the case.

CHILDREN WITH INOPERABLE CONGENITAL HEART LESIONS

The two principal groups of patients with congenital heart lesions which are not surgically correctable are those whose lesions are technically too difficult to correct; for example, persistent truncus arteriosus and single ventricle; and those whose lesions are technically correctable but who have complications which make successful operation extremely unlikely; for example, atrial or ventricular septal defects with pulmonary vascular obstruction of such a degree as to make the dominant shunt right to left.

Corrective surgery cannot be anticipated for either of these groups of patients in the near future at a low operative risk. The parents must be told the truth in general terms and if the patient is old enough to appreciate the problem he too should be told that his heart is not as efficient as that of the average child and that his activities may have to be restricted. If a child is cyanotic the reason for his color should be explained. Parents and the patient should be told that medical science is advancing rapidly, that operations impossible ten years ago are now being done every day and that we must anticipate further great improvements. The child should be seen by his physician at least once or twice a year, and more often if his physical or psychologic well-being makes this necessary. Specific therapy directed to the heart and circulatory system will depend on the development of symptoms or signs of cardiac decompensation. Children with congenital heart disease not correctable by operation must be guided into occupations and careers which are in keeping with their physical, mental and emotional abilities. In the majority of cases this means a sedentary occupation; the greater the child's intellectual development and vocational training, the greater will be his chances of success.

Endocardial Fibroelastosis: Many children when first examined have cardiomegaly without murmurs and the electrocardiogram shows evidence of left ventricular overload. Endocardial fibroelastosis will be the correct diagnosis for a large percentage of these patients but there is no clinical or laboratory test to prove the diagnosis. There is always a chance that infectious myocarditis is the underlying disease. Time and digitalis often are required to solve this dilemma. Such patients must be restricted from any undue exertion but if they do not have congestive heart failure they may lead a

quiet and subdued life for several months while their progress is being observed. In many cases the size of the heart will not diminish but will increase; intractable failure or sudden arrhythmia may result in death. Only at necropsy can the diagnosis of endocardial fibroelastosis be proved. In other cases the size of the heart may return to normal limits and the diagnosis of infectious myocarditis may be assumed to be correct, although without the isolation of a specific causative organism this is not known for certain. Because of the danger of early death from endocardial fibroelastosis and because the heart usually returns to normal size in a few months after infectious myocarditis, patients with large hearts and no murmurs, in whom pericardial effusion can be excluded, should be followed for months or years. If there is evidence of cardiac decompensation or of cardiomegaly to even a moderate degree physical activity should be modified accordingly.

ASSOCIATED ANOMALIES

Children with congenital heart disease may suffer also from associated anomalies either congenital or acquired. Some may have cataracts; some are mentally retarded and others may have varying degrees of kyphoscoliosis or hemiplegia. Whatever the associated anomalies, they must be considered in the over-all treatment of the child if optimal results are to be achieved.

Over-all Problems of Rehabilitation

In the over-all problem of rehabilitation of children with congenital heart disease[1] three main facets must be considered, namely: (1) general medical management, (2) physical activity and (3) social and economic factors.

General Medical Management: Medical care at home must involve not only specific treatment directed toward the heart itself but also the prevention of possible complicating factors such as bacterial endocarditis. Bacterial infections should be treated promptly and vigorously and antibiotics should be administered as a prophylactic measure for tooth extractions and minor surgical procedures including catheterization of the bladder and incision of boils, and certainly for any major surgical procedure.

A good practical approach is very necessary in caring for handicapped children. One of the greatest drawbacks to intelligent care by parents is the flood of advice given by their friends. Advice that such-and-such a clinic or that Dr. So-and-So works wonders with this type of case can send the family traveling around the country and spending beyond their means. After the child has been seen in a local clinic and if it is decided that further studies are indicated, he should be referred to a good center for complete investigation. If, at the end of this examination including special tests that may be required, the parents still request a further opinion, the history, findings at physical examinations, electrocardiograms, roentgenograms, catheterization data, angiograms or any other relevant data should be forwarded to the center of choice. In most cases a careful perusal of the data will allow the experienced pediatric cardiologist to decide whether or not the family is justified in spending more money for further investigations. A large number of patients with operable lesions may be detected but, on the other hand, records also are returned with the sad news that nothing can be done.

One valuable service a physician can provide for parents is to correct misconceptions concerning feeding of babies with congenital heart disease. In general, a baby with congenital heart disease requires the same food as other babies. Feedings may have to be given more frequently and in smaller quantities to babies who are dyspneic or who have anoxic spells. Additional iron may be indicated after the age of six months for cyanotic babies who, because of fatigue and respiratory distress, do not take solids well. Additional vitamins over and above those prescribed for normal babies, or so-called tonics are not necessary.

Physical Activity: Several details must be considered in a program of physical activity for any affected child. These are: (1) the seriousness of the disability including complicating factors such as hemiplegia, (2) the home environment, (3) the sympathy or otherwise of the parents, (4) the climate in which the child lives, (5) the distance that the child has to go to school, (6) the availability of transportation and (7) the temperament of the patient. These factors and many more will modify the program for each individual patient. The program should be specific and should not consist of a series of vague generalities when the physician himself is unsure and the family is confused.

The degree of physical activity which can be enjoyed by each patient depends largely on his capacity for exercise rather than on the nature of the underlying disease. Children with severe

cyanotic congenital heart disease will become breathless before they have accomplished much exercise; the same will apply to patients in congestive failure whatever the underlying cause. Patients with aortic stenosis must be restricted physically because although able to carry out vigorous exercise their efforts may result in sudden death. Patients with coarctation of the aorta and hypertension in the upper extremities are probably better off restricting themselves from strenuous activities until after surgical removal of the coarcted segment. The well-known association of coarctation of the aorta with small aneurysms in the intracranial circulation makes subarachnoid hemorrhage a real danger.

Economic and Social Considerations: Congenital heart disease of a serious nature will not get better spontaneously except in a small number of patients. Rather, the symptoms are likely to become more marked and the disability greater with the passage of time. This gradual worsening of the physical state usually is accompanied by a continuing drain on the economic resources of the family, often causing tension within the family and a severe degree of emotional stress in the patient. Under these difficult physical and emotional circumstances a child may have considerable trouble adjusting socially and may become introverted or openly defiant and hostile. It is hard for a child to understand why he is different from others, why his skin may be blue and why he is being taken periodically to the doctor's office. The fears and neurotic traits of children are more difficult to analyze than those of adults but they may be just as real. Children, especially the older ones, who have been subjected to cardiac catheterization and cardiac surgery which may or may not have been completely successful may have a real fear of dying. Appreciation of this fact helps in understanding a child's behavior and may create a bond of sympathy between the physician and his patient.

Adequate care of a child's medical and emotional needs improves his general feeling of well-being and makes his social adjustment much easier. The important aspects of social adjustment for handicapped children involve interpersonal relationships, education and, ultimately, a vocation which must be tailored to the child's anticipated abilities and potential. In this last regard a vocational counselor may be of considerable assistance. While attending to these many aspects of a child's welfare the persons near a child must not forget that whatever they do in an effort to care for a patient they must preserve the personal dignity of that patient and make him feel that he belongs in the family and in the community. In this way he can be encouraged to make the best of his physical and mental abilities.

Many questions are asked by the family of a child with congenital heart disease. Each of these questions should be answered honestly and intelligently by the physician. Each question illustrates the fears of the family and an incorrect answer can lead to considerable disappointment and expense. The physician should anticipate these questions and be prepared to answer them. The following questions represent some of those more commonly asked:

Will he grow out of this?
Will an operation cure him?
Will medicines help?
How long will he live?
How much will he be able to do?
Will his symptoms progress?
Should we move to a different climate?
How much should we restrict him?
Will a special diet help?
If we have other children, will they also be affected?
Why did this happen to us?

A frank discussion with the parents should enable the physician to answer these questions honestly and he should not let the parents depart while still full of doubts. Obviously, if a correct diagnosis has not been made and if the physician is not fully conversant with the natural history of a particular disease process his advice is not going to be helpful. A frank discussion with the parents will not solve their problems but will help them to understand them. In a number of cases feelings of guilt and anxiety will be alleviated.

Summary

This paper has attempted to summarize many of the everyday problems associated with the rehabilitation of children with congenital heart disease. The need for a planned cooperative effort on the part of all those entrusted with the child's care has been stressed and certain specific problems associated with patients treated surgically or medically have been discussed.

Recommended Reading

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Survival and Rehabilitation in Coronary Occlusion

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THOUSANDS of daily bona fide attacks of coronary occlusion attest to the magnitude of the problems produced by this type of heart disease.[1–3] I will not attempt to cite exact figures on incidence, nor write of the life years or employment years lost after coronary occlusion; rather, I will concentrate on survival following coronary occlusion and the importance of rehabilitation and return to work.

The literature on survival and rehabilitation following coronary occlusion is very large.[4–67] Although incomplete, the bibliography will include, nevertheless, a more than adequate list of references for those who wish to pursue the subject further. Moreover, I will discuss chiefly acute coronary occlusion. Excellent reviews on general rehabilitation for heart diseases have been published.

EPIDEMIOLOGY AND STATISTICAL ASPECTS OF CORONARY OCCLUSION

It is almost impossible to obtain accurate figures on survival and rehabilitation following coronary occlusion. Broad epidemiologic surveys are essential to establish more reliable statistics, but even these are subject to question. Thus, patients who have "silent" attacks of coronary occlusion and keep on working may be missed completely. The diagnosis may be made only by chance months or years later when an electrocardiogram, taken during a routine check-up or other examination, discloses findings of old myocardial infarction. In these instances the victim or his family, on questioning, usually recall that he stopped work for a day or two or a week, because of "indigestion" or a "cold." Then there are *sudden deaths* which occur at home, no autopsy is performed and the exact diagnosis may not be recorded when the doctor completes the death certificate. Often the diagnosis is a guess. Coronary occlusion may be diagnosed when actually a cerebrovascular accident was the cause of death and vice versa. Furthermore, the question of *diagnostic skill* arises. The correct diagnosis is frequently made more accurately in a locality where doctors are experienced in coronary disease than one in which they have little opportunity to perfect themselves in the diagnosis of heart diseases.

In reviewing statistics the *years encompassed are important.* The diagnosis of coronary occlusion between 1920 and 1925, perhaps even to 1930, was uncertain. It was not made frequently enough since the disease was still unusual. In 1940, the disease had become common and the diagnosis was much improved; in 1950 to 1960 the diagnosis was still sharper. In the early days of the three and then the four lead electrocardiogram the diagnosis of coronary occlusion was not made as accurately as it is now with the twelve lead electrocardiogram. The *survival rate*[4–23] of the attack of acute coronary occlusion presents more problems. When should one begin to calculate it? Wilson[68] believed that the most serious time is the first half hour. As the days pass the outlook for survival and for good recovery improves. Where shall one then use statistics on survival, after the first half hour of the attack, or after the first 2 or 3 months, or even at the end of the first year? Authors have employed these different end points and hence statistics on survival and rehabilitation are not comparable. They can be made comparable only when thorough epidemiologic studies are undertaken.[45,69–78]

Differences have been recorded in the *various races*, e.g., the Negro, the Oriental and the Caucasian, in regard to the incidence and mortality rate of coronary occlusion. There may also be variable results in different *socio-economic* classes. The diagnosis is made more certainly in private practice. The private patient fares

better because he sees a physician more often. The poor person is more apt to neglect himself. Hence, the statistics for these groups should perhaps be kept distinct.

Another variable in the evaluation of the epidemiology of coronary occlusion is the *consultant*, that is, the internist or the cardiologist. If he sees only the severe case, his statistics may reveal a greater mortality and a lower subsequent survival rate than otherwise. Again, he may never see the patient who succumbed suddenly, that is, immediately or within the first twelve to twenty-four hours, or even in the first week or two.

Factors in Survival and Rehabilitation

Age and sex are factors affecting survival and return to work after coronary occlusion.[79] The question of age must be considered in determining the mortality rate within the first month or two, the survival rate in the following years and rehabilitation following recovery. If coronary occlusion develops in a man of forty, his life span ordinarily might be another thirty-five to forty years, whereas the life span of a man of sixty may be only fifteen years. Another way of making this point is to recall the over-all mortality rate for a given age. In 1,000 people sixty years old the mortality rate will be higher than in 1,000 men of forty; women will have still a lower rate. These factors, too, affect the statistics of not only the immediate and subsequent mortality and ability to return to work, but also the life years or the employable years lost after the attack.

Severity of Attack: A previous attack, the presence of heart failure, shock, enlargement of the heart, serious arrhythmias, pulmonary infarction, peripheral or cerebral embolism and possibly hypertension could influence immediate mortality rate, survival and rehabilitation. In other words, the degree of severity of the acute attack is important.

Hypertension: The relationship of hypertension to survival and return to work is not clear.[79–82] First, there are many definitions of hypertension. Then, hypertension seems to vary between men and women. It appears to be a factor in the cause of coronary occlusion in women, but in men the relationship is not too clear. It appears probable that the presence or absence of hypertension does not affect the immediate survival rate of coronary occlusion; yet, one would think, and the literature seems to indicate it, that patients with severe hypertension will not survive as long, or be rehabilitated as easily, as those with no hypertension or only mildly to moderately elevated blood pressure.

Type of Employment: In return to work the type of employment is a factor. The white collar man, the professional man, the businessman and the executive are much more apt to return to their jobs because they can control their duties and avoid undue mental, emotional and physical stress. The ordinary worker, the laborer, the store worker may not be able to do this. In between these groups are the white collar and office worker.

The disabled man of sixty or the woman of fifty is entitled to *social security*. He or she is less apt to desire to return to work because of this income.

Nomenclature and Differential Diagnosis of Coronary Diseases

Another difficulty in studying survival rate and rehabilitation following coronary occlusion has been the nomenclature of the acute coronary heart attack. In the past any change in the electrocardiogram was labeled coronary thrombosis or occlusion. Even severe chest pain or shock might be mistakenly so diagnosed. Contrariwise, if a somewhat atypical feature was found, the episode of coronary occlusion might falsely be labeled some other condition. There is a great difference in heart attacks, that is, between acute coronary insufficiency without occlusion[83,84] and coronary occlusion or thrombosis. In this paper I consider only acute coronary occlusion with myocardial infarction and interchangeably employ the expressions coronary occlusion and thrombosis.

In at least 95 per cent of the cases one can distinguish between these two types of acute coronary episodes clinically, electrocardiographically and pathologically. This distinction has not been clearly made in many discussions of coronary episodes. This accounts for some prevailing misconceptions. Effort, for instance, plays an unquestioned role in acute coronary insufficiency without occlusion and may even lead to death; but it is not a factor in coronary occlusion.[85–88]

Attacks of acute coronary insufficiency without occlusion vary widely in degree.[83,84] Although the severe form may even cause death, it is a relatively benign process as an over-all category in contrast to coronary occlusion. The pain of acute coronary insufficiency without occlu-

sion, unlike the simple, transient episode of angina pectoris, is usually severe and prolonged. The inadequacy of the coronary circulation far exceeds functional limits and frequently results in demonstrable pathologic changes. These consist of infarction or focal areas of necrosis confined to the subendocardial region and papillary muscles of the heart, in contrast to the through-and-through infarction which results from coronary occlusion.

In coronary occlusion the usually very severe pain in the chest or arms is apt to be accompanied by fall in blood pressure, shock, nausea and vomiting, leukocytosis, fever, pericardial rub, elevated sedimentation rate and high serum transaminase levels. Transmural infarction with endocardial and pericardial involvement is demonstrable on pathologic examination, unless the patient died within twenty-four to thirty-six hours of the onset.

There is a clear distinction electrocardiographically between the two conditions. Because of practically exclusive subendocardial involvement in acute coronary insufficiency without occlusion, depression of the RS-T segment or T wave inversions or both are seen, but no deep Q waves are discernible. There are no dramatic RS-T elevations. In acute coronary occlusion with through-and-through infarction, one finds deep Q waves and RS-T elevations progressing into inverted T waves. The RS-T elevations are associated with pericardial injury.

Clearly, if correct figures are desired in a study of the immediate mortality rate, survival rate and rehabilitation during or following recovery from acute coronary occlusion, recourse to *epidemiologic investigation* must be made.[45] A city of 100,000 population in which every single individual is followed yearly and autopsies performed on every dead person would be the goal. This might be impossible, but fairly good starts have been made in the Albany, California, Chicago, English, Framingham and South Dakota studies.[71–78]

Mortality and Rate of Survival in Coronary Occlusion

What are the prospects for survival after recovery from the attack of coronary thrombosis?[23–64] How many patients live one, five, ten, twenty or more years? How many make a fair recovery, a good recovery? Is there such a thing as a complete recovery, functional or anatomic or both?

The old statistics are unreliable. From 1920 to 1940 no distinction was usually made among angina pectoris, coronary insufficiency without occlusion and coronary occlusion. Chest pain with any electrocardiographic change was simply labeled "coronary thrombosis." At present the immediate mortality varies from 15 to 30 per cent in hospital cases but is still slowly diminishing. Patients in their first attack treated in private practice have the best prognosis. Their mortality is between 3 and 5 per cent. This striking difference is undoubtedly due to the fact that sicker patients are more likely to be found on the wards of a hospital.

Survival Rate: If an immediate over-all mortality rate of 20 per cent for the first two months is assumed, how many will survive one or more years? Since coronary thrombosis is a disease in which the treatment and prognosis must be individualized, a great many variables must be considered. In general, those who recover but who during the acute stage or subsequently had heart failure, shock, enlarged heart, rapid heart beat, pulmonary infarction or embolism, serious arrhythmias or severe angina pectoris, fare badly; their mortality rate is probably about 10 per cent per year. At the end of five years, therefore, only about 30 per cent of these patients will be alive; at the end of ten years, very few, if any, survive. But of those who have made a good functional recovery from the acute coronary thrombosis, fewer than 5 per cent will succumb each year. After five years, therefore, at least 55 per cent will still be alive; at the end of ten years, 30 per cent; at the end of 15 years, perhaps 5 to 10 per cent may be living. These approximations are based on our own figures and those of the literature cited.[23–64]

The *insurance companies* have presented statistics on those who are disabled by coronary thrombosis.[36,39,45,57,58] Their figures are important since their follow-up continues to the death of the patient. Of course, theirs is a select group, that is, people who have insurance for complete and total disability. Many may not be really disabled completely and could perform some work, but do not because the payment is only for "complete and total" disability.

Functional Recovery Following Acute Coronary Thrombosis

From the time of Herrick until about 1930,

a patient who had an attack of coronary thrombosis was considered to be totally and permanently disabled. He, his family, and even his physician, were all constantly apprehensive, and his least physical activity engendered much concern. Resumption of work was, therefore, never considered. Unless the patient fortunately had enough disability insurance, the burden of earning a livelihood necessarily fell upon wife, child, parent or state. And what a fortune the insurance income seemed in those days. Who would be rash enough then to urge a patient to forego this unearned income and risk death by returning to work? Few, indeed. Only a handful of us then insisted that work was good for both body and soul.

Today, it is generally agreed that most patients who have recovered from an attack of coronary thrombosis may resume light work two or three months after the attack and gradully increase the work. *Complete functional recovery*[88] from an attack of coronary thrombosis now occurs frequently enough that even some insurance companies have begun to alter their attitude toward the disease.[36,39,45,57,58] They no longer automatically reject the applicant with a history of an attack as a totally uninsurable risk. Of course, the risk *is* greater, and the annual premium is increased.

We believe it is important for the patient to return to work. This is essential for morale and necessary for physical well being. A man should enjoy work. "*Unstructured leisure*" has now descended on us because of modern machines and automation and the desire of men and women to work fewer and fewer hours a week. "Unstructured leisure" has become a national problem of the first order for the nation and for the doctor. It leads to unhappiness, boredom, divorce, crime, juvenile delinquency and other social disorders. Occupied men and women are the happiest. We plead not for frenetic work but for leisurely occupation. It is the pace that kills, not the number of work hours per week.

Functional Recovery and Return to Work: My associates and I made a survey of 500 patients who had survived acute coronary occlusion by one year or more.[41,61,88] The series comprised 90 per cent private and 10 per cent ward patients. The diagnosis was confirmed electrocardiographically by the presence of Q waves and S-T elevation, indicating through-and-through infarction. Following the acute attack, 41.8 per cent of the 500 patients with coronary occlusion made a *complete functional recovery*, i.e., they were asymptomatic. A similar percentage, 42.6 per cent, experienced mild anginal pain or dyspnea on exertion, but their activity was only slightly restricted if at all. Combining these two groups, it is evident that over four of five patients made either a satisfactory or excellent recovery. The remaining patients included 10 per cent who experienced moderate angina or dyspnea and 5.6 per cent who had severe or intractable symptoms.

It is interesting that in the group of 209 asymptomatic patients who had completely recovered, 177 (84.7 per cent) presented objective evidence of the previous myocardial infarction in the electrocardiogram, roentgenogram or both. Over two-thirds showed mild to moderate cardiac enlargement and electrocardiographic alterations and thirty-two patients showed marked changes, with a definite diagnosis of ventricular aneurysm in twelve. In spite of these factors, the subsequent mortality rate was only 15.3 per cent in these 209 asymptomatic patients. Two-thirds had already survived over five years, and 22.6 per cent over ten years. Two-thirds of the patients were working full time and 20 per cent part time.

In the group of 213 patients who had made satisfactory recovery, i.e., they experienced mild angina or dyspnea, the length of survival, mortality rate and percentage returning to work were only slightly less satisfactory than in the previous asymptomatic group.

In the entire series of 500 the average period of survival was 7.2 years. Three-fourths of the patients were still alive; 51.7 per cent survived over five years and 17.3 per cent over ten years. Eleven were alive over fifteen years and 70 per cent were working.

Clearly then, we are convinced that many patients with a coronary occlusion do recover completely with the passing years. Their chest pain, dyspnea and weakness either disappear immediately or gradually following their attack. We now have seen scores of patients without symptoms for two to ten or more years after an acute coronary occlusion. They live completely normal lives, often work long hours under tension, and occasionally even perform heavy manual work. They still *may* show an abnormal electrocardiogram, often a bad one. In fact, rarely does an electrocardiogram return completely to normal at the end of the first year.[89–91] Whether complete anatomic restitution takes place in the coronary arteries,

we do not know, but with time, thrombi are recanalized. A good collateral circulation, however, is probably more important than the recanalization of a thrombosed artery. In any case, restitution of the coronary circulation appears to occur clinically.

Guides to Degree of Functional Recovery: We have found, like many others, that the *symptoms* of the patients are the best reliable guide to *rehabilitation* of the patient who has recovered from a coronary occlusion.[11,60,61,88] If one has a patient whose story is not colored by questions of insurance or litigation, his complaints are the most important. In other words, if the patient has shortness of breath, an anginal syndrome or evidence of heart failure, his return to work must be qualified. On the other hand, the patient without symptoms on ordinary exertion or excitement has probably made a good to complete functional recovery. Even a patient with an enlarged heart, in fact, occasionally a patient with both an enlarged heart and ventricular aneurysm, may carry on regular work, although not necessarily hard work.[88] Such patients may find more difficulty in traveling to work than in actually working on the job. To help solve this problem of transportation, Levine[92] has provocatively proposed that the man earning $75 to $100 a week may benefit by taking a taxi to and from his work. Why should not "taxi pools" to work be arranged by the local heart associations for the partially disabled people?

Can a patient with coronary occlusion ever return to hard labor, e.g., as a longshoreman or truckman? In general this should only rarely be condoned. A patient who has recovered from an acute coronary occlusion presumably has severe coronary disease, and therefore should avoid extremes of physical, mental and emotional stresses. These undue events can readily precipitate acute coronary insufficiency without occlusion. This is not to say that the patient who has recovered from an acute occlusion should not return to employment. He should indeed work, but within the limits of his cardiac reserve. However, all of us have on rare occasions seen such patients go back to heavy manual labor or stressful occupations and do well.

Coronary Occlusion in Physicians: Since the readers of this article are physicians, it will be of interest to inquire whether coronary occlusion is a doctor's disease. The insurance companies, and Morris in England, have indicated that doctors suffer more coronary disease than is their due by proportion of the population.[37,51,93] We and others doubt this. The doctor is more apt to make a prompt diagnosis of coronary disease in himself than in an ordinary patient. However, it is also possible that excessive physical exertion and the crowded, tense lives of many physicians may precipitate episodes of acute coronary insufficiency without occlusion to a greater extent in those with coronary artery disease than in people who lead more tranquil lives. I do not concur that coronary thrombosis is a doctor's disease and hope to present more proof in the near future.

Rehabilitation of Physicians: I have had scores of patients, including physicians, who had suffered a coronary occlusion and who carried disability insurance good only until age sixty. In their fifty-ninth year they were faced with the problem whether they should stop working and gain a disability pension, or wait and lose it. These were patients usually with symptoms of mild to moderately severe angina pectoris. In almost every case I persuaded them to keep on working at a sensible pace, and I cannot recall any who regretted following my advice. Occasionally, even a few physicians who made house calls and climbed a few flights of steps kept working profitably and, more to the point, happily. They climbed stairs very slowly and often used a nitroglycerin tablet before they began to climb.

Relation of Effort to Onset of Coronary Occlusion

Since we urge the patient who has recovered from a coronary occlusion to work, I would like to discuss the precipitating factors of acute coronary occlusion, and specifically, the *relation of physical exertion and occupation to the onset of coronary occlusion.*

For years, it was believed that extreme physical exertion or unusual emotional tension precipitated coronary occlusion. We do not believe this.[84–87] Hard work, especially under stress, *ipso facto*, does not cause coronary disease; although in persons who already have underlying coronary artery disease, it may precipitate attacks of angina pectoris and acute coronary insufficiency without occlusion.[82,83,87] In our own studies of the last twenty-five years,[84–87] proportionately less coronary thrombosis was found in laborers who work hard physically than in sedentary workers. Investigation of the type of occupation, hour and day of

onset of acute coronary occlusion, activity and inactivity, reveals that neither occupation, effort, nor rest play a role in this form of heart attack.

From our numerous statistics we concluded (1) that neither effort nor the stress and strain of modern life precipitate acute coronary occlusion; (2) that coronary occlusion occurs with equal frequency in all classes of society and in all types of occupations, perhaps slightly less in those of a physically laborious nature; and (3) that coronary occlusion is the end result of an atherosclerotic process and occurs independently of external influences. Furthermore, we concluded that the increased emotional stress and strain of present day working and living did not tend to produce coronary artery occlusion. The high strung and the phlegmatic person is equally susceptible to it.

Workmen's Compensation Problems: Since neither physical strain nor emotional stress is a direct precipitating cause of coronary thrombosis, the practice of awarding workmen's compensation for this disease is wholly unjustified. On the other hand, in cases of angina pectoris and acute coronary insufficiency without occlusion, strain and stress are commonly precipitating factors and may, therefore, be compensable in certain instances.

The question of workman's compensation is a difficult, complicated problem.[94–96] The unions want their members given every possible "break." The employer and the compensation insurance companies are utterly confused by the diversity of medical opinion concerning the relationship of work and occupation to coronary occlusion. Consequently, the employer hesitates to hire a man who once had had a "heart attack," since his firm will often be held responsible for further trouble. At present, it is our opinion that the state should care for the man or woman who develops illness while at work. This will be equable to all and medical opinion will not be influenced by union or employer. Such unbiased scientific opinion is essential in the study of atherosclerosis and coronary occlusion.

Rehabilitation during Acute Attack

Although the treatment of the acute attack of an acute coronary artery occlusion is not the subject of this paper, it has much to do with return to work. In our own treatment of patients during an acute coronary occlusion, we follow the procedures of Harrison,[97] Dock[98] and Levine.[99] If the patient has had only a mild attack and is doing well, he will be permitted to use a commode the second or third day or even go to the bathroom provided it is only a few feet away. He may sit out of bed in a few days. The patient is always helped to the chair, to the commode and to the bathroom. We have him out of bed at the beginning of the fourth week as long as the patient desires. He returns to bed whenever he is tired. By the end of the fourth week he begins to walk slowly and can go home if he has been hospitalized.

We do not hesitate to allow return to work at the end of two months. Occasionally, in very exceptional cases, this occurs even in four to six weeks from the day of the attack. He begins gingerly, at first for an hour or two a day. This would, of course, be for a desk job. Each case must be individualized. The patient who loves his work and is completely relaxed at it can return to work and do better than if he were kept at home, repressed, frustrated and worried to death about his business. The other side of the story, it should be obvious, is the patient who is completely disabled for months or permanently. Although this is uncommon, it does occur.

Illustrative Case Histories

Case histories exemplifying satisfactory to complete functional recovery will be presented. We could cite case after case of patients who returned to work successfully for years following their coronary occlusions. For example, a busy executive (J. S.) suffered bona fide attacks of acute coronary occlusion in 1947 and 1949. Now seventy-two years old, he works full time, follows fairly long hours and puts an unusual amount of zest into his occupation. It is eleven years since his second attack and thirteen years after his first.

An internationally famous surgeon (Dr. H. M.) suffered one definite coronary occlusion twelve years ago and subsequently two episodes of acute coronary insufficiency without occlusion. He has had no complaint for the last three years. At the age of seventy-six he performs surgery and leads an active life; he works harder than the average healthy man of that age.

Another patient (M. N.) was first seen in 1938 at the age of fifty. He had suffered a coronary occlusion either in 1931 or 1933. He had a definite anginal syndrome when first examined in 1938. His electrocardiogram showed deep Q waves in leads II, III and aVF. Now in 1960 at the age of seventy-two he is fairly active, follows moderation and is occupied in business. If he were to perform strenuous physical exertion, he would have angina;

so he avoids it. Another disability—perhaps an asset—is severe bronchial asthma. At any rate deep Q waves in leads II, III and aVF with RS-T depressions have probably always been present in his electrocardiogram for twenty-seven or possibly twenty-nine years after the coronary occlusion. Nevertheless, the patient leads an active, productive life.

An active advertising executive (N. F.), now sixty-four years of age, sustained an acute coronary occlusion fifteen years ago. He has no complaint and continues to work hard in the advertising business.

A laryngologist (Dr. B. G.) worked and operated until his death at the age of seventy-one years, although he had suffered two attacks of acute coronary occlusion fifteen and nine years previously.

Another man of seventy-three (M. N. P.) suffered an acute coronary occlusion seventeen years before, at the age of fifty-six years, and mild angina developed at the age of sixty-five years. Despite this mild anginal syndrome he still works and does almost everything.

Summary

The importance of a patient's return to work following recovery from an attack of acute coronary occlusion is emphasized.

Mortality and survival rates for the years following the attack were studied and found inaccurate because of diagnostic and classification problems, viz., the matter of "silent" attacks, the correct diagnosis in sudden deaths, diagnostic skill, the decade encompassed in a particular study, the survival rate of the attack itself, the question of a three or four lead versus a twelve lead electrocardiogram, race or color of the patient, the socio-economic status, the severity of the case seen by the internist or cardiologist, age and sex, the severity of the acute attack, the question of hypertension and the nomenclature of the acute coronary heart attack.

To obtain more accurate figures, broad *epidemiologic surveys are essential.* In return to work, the type of employment must be considered.

If we assume an immediate over-all mortality rate of 20 per cent for the first two months, in general, those who recover but suffer a severe attack, that is, one with heart failure, shock, enlarged heart, rapid heart rate, pulmonary infarction or embolism, serious arrhythmias or severe angina pectoris, do badly. Their mortality rate is probably about 10 per cent per year. Of those who have made a good functional recovery from the acute coronary thrombosis, fewer than 5 per cent will succumb each year. Altogether, four of five patients make either a satisfactory or excellent recovery.

Return to work is essential for the patient's morale and physical well being. "Unstructured leisure" has become a national problem. We are not pleading for frenetic work but for a more leisurely occupation. Symptoms of the patient remain the best reliable guide to his rehabilitation. "Taxi pools" should be arranged by the local heart associations for the partially disabled heart patient.

Our studies have indicated that (1) neither effort nor the stress and strain of modern life precipitates acute coronary occlusion; (2) coronary occlusion occurs with equal frequency in all classes of society and in all types of occupations, perhaps slightly less in those of a physically laborious nature; and (3) coronary occlusion is the end result of an atherosclerotic process and occurs independently of external influences. Since neither physical strain nor emotional stress is a direct precipitating cause of acute coronary thrombosis, the practice of awarding workmen's compensation for this disease is wholly unjustified, yet numerous such awards are made daily by referees.

We have painted an optimistic picture for a patient's return to work following his recovery from acute coronary occlusion. It is necessary for the physician to encourage patients to return to work; in fact, it is his moral obligation to do it. At work the patient is happier and relieved of the dangers of boredom and frustration.

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Rehabilitation and Employment of Industrial Workers with Cardiovascular Disease*

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THE EMPLOYMENT OF persons with cardiovascular disease has become an increasingly important problem in industry. Employment in a job suited to the subject's skills and within his physical, mental and emotional capacity is one of the major goals in rehabilitation and must be considered from the standpoint of the patient, the employer and the physician. In this article I will discuss these problems briefly and report our experience in selective placement and rehabilitation of industrial employees with cardiovascular disease at the Gillette Safety Razor Company in Boston, Massachusetts.

In evaluating the ability of a subject to engage in a specific job a great amount of information may be required.[1,2] The following are important *from the patient's standpoint:* (1) Does the person really have cardiovascular disease and if so, what limitations does it place on his ability to work; (2) could the disease be caused or aggravated by an industrial injury or by the strain of unusual effort; and (3) will the failure to return to work do as much to aggravate the disease process as returning to previous labors?

Factors important *from the standpoint of the employer* are as follows: (1) Will the worker with cardiovascular disease endanger the safety of fellow employees; (2) will the subject produce at a profit; (3) is the value of the worker's experience sufficient to justify employment in spite of added insurance risks; (4) what effect will the decision have on the morale of other employees; and (5) what effect will employment of the subject have on the seniority system and the right to retain a job in spite of handicaps?

From the standpoint of the physician questions such as the following must be answered: (1) What are the mental, emotional, physical, social, vocational and economic assets of the patient; (2) from what cardiovascular disease does the patient suffer (etiologic, anatomic, physiologic, functional and therapeutic classifications); (3) does the patient understand the nature of his disease and what limitations, if any, it imposes on his ability to lead a normal life; (4) what are the requirements of the patient's job; (5) what are the nonoccupational stresses such as obesity, diet, smoking and recreational habits; and (6) what effect is employment likely to have on the course of the patient's disease as well as his over-all social and emotional adjustment?

In our studies we have attempted to answer some of these questions for the employer, the employee and the physician. In the plant there are about 2,000 employees. This industrial work is light to moderate in nature and composed mostly of skilled or semiskilled machine operation; concentration is important. With the permission of the management of the company we have carried out extensive, long-term clinical observations on the employees with and without cardiovascular disease.

CARDIOVASCULAR DISEASE AMONG EMPLOYEES

The number of employees with different categories of cardiovascular disease are listed in Table I. Many of these persons have been personally observed over an eight year period.

Coronary Artery Disease: Among the fifty-two employees who suffered coronary thrombosis there were eleven executives and forty-one workers. Seven of these executives are still working and have a total of thirty-five years of productive employment since their initial attacks of coronary thrombosis. In the total group (fifty-two cases) there have been 269

* From the Medical Department, Gillette Safety Razor Company; Department of Medicine, Medical Associates of the Massachusetts Memorial Hospitals; and the Department of Industrial Medicine, Boston University School of Medicine.

TABLE I
Cardiovascular Disease Among Industrial Employees

Diagnosis	Number of Employees
Arteriosclerotic heart disease with coronary thrombosis	52
Hypertension and/or hypertensive cardiovascular disease	130
Rheumatic heart disease	34
Congenital heart disease	3
Total	219

years of productive employment by persons since their initial coronary thrombosis. About 64 per cent of these workers have been employed for three years since the coronary thrombosis, 52 per cent have worked at least five years and 11 per cent have worked at least ten years since the initial attack.

Eight employees with angina pectoris and no objective evidence of coronary thrombosis have contributed a total of thirty-five years of effective employment or about 4.4 years per person, since the onset of clinically manifest coronary artery disease.

It is of interest to note that in our fifty-two cases of acute coronary thrombosis, no attack occurred while the patient was on the job. In less than 10 per cent the acute episode was associated with severe exertion and in over 90 per cent the attack occurred when the subjects were either resting or performing ordinary activities at home.

There are nine employees who have died as a result of coronary artery disease. Three workers and one executive died in the initial attack; three workers died after subsequent attacks but they had worked eight, ten and fifteen years, respectively, after the first episode of coronary thrombosis; and two workers died within two years of the initial attack.

Of the group that retired (ten cases), there were two executives who did so voluntarily, two workers who did so on advice from their doctor (three and thirteen years after their initial attacks) and six workers who had routine retirements at age sixty-five.

Hypertension: There are 130 employees with hypertension and/or hypertensive cardiovascular disease. The great majority of these had symptomatic hypertension unless under appropriate treatment. In this group five subjects have died during our eight year period of observation, eight have retired at age sixty-five and the remainder are still working effectively.

Rheumatic Heart Disease: There are few studies available on the fate of the employee with this heart disease, although the problem of collective disability will probably be of major concern in the future. Of the total group (thirty-four cases) observed over an eight year period, five are dead, one was retired prematurely, twelve have been discharged for nonmedical reasons and sixteen continue to work. Ten of the latter are in the worker group and problems related to their continued employment present a real challenge. Although we do not believe that employment alters the prognosis for these people, our experience with this small group indicates that they are not good risks for this type of employment.

Occupational Accidents and Injuries

There have been few studies of the susceptibility of workers with cardiac disease to occupational accidents and injuries, although this is often a major factor in their employment or reemployment.

In a previous study[2] we noted that among unselected employees with no cardiac disease the incidence of major accidents was 1 per cent and of minor accidents 2 per cent. There have been no claims for death due to cardiac disease or claims for aggravation of existing heart disease. The possibility of such claims is management's greatest fear.

There has been no evidence that a worker with cardiac disease, properly placed, is a danger to himself or to his fellow employees. The increased incidence of minor accidents reported (14 per cent as opposed to 2 per cent for the average worker) probably reflects more the desire of the worker with cardiac disease to maintain his health than it does an actual increased liability to accidents. It is to be noted that the groups with arteriosclerotic and hypertensive cardiovascular disease had no major accidents in spite of the fact that they are generally thought to represent the major risks in industry. More recent studies of the groups show even less incidence of minor accidents and no major accidents or injuries among cardiac workers.

Work Performance

It is important to note that studies of the cardiac patient's functional capacity do not

TABLE II

Comparison of Absenteeism in the General Plant Employee and those with Cardiovascular Disease

Population Group	Average Days Lost Per Year Per Employee		
	1955	1956	1958
Average employee	11.4	11.3	10.6
Men	8.9	9.0	8.7
Women	15.3	15.3	14.2
Employee with cardiovascular disease			
Arteriosclerotic heart disease	22.1	13.3	24.4
Rheumatic heart disease	14.5	13.6	19.5
Hypertensive heart disease	11.9	10.6	17.7
Essential hypertension	...	11.3	11.9

TABLE III

Comparison of Long Term Absenteeism Due to Disease Causes

Disease	Absences (%)	Days Lost (%)	Average Time Lost Per Case (weeks)
Gastrointestinal	16.7	17.5	8.2
Respiratory	14.7	10.7	5.9
Accident	12.7	9.7	6.6
Musculoskeletal	10.2	10.2	9.2
Cardiovascular	7.7	12.2	11.4
Female reproductive	6.5	10.5	9.9
Neuroses	5.2	6.5	9.7

necessarily indicate what his work performance will be. This is an important factor to industry in hiring or rehiring the worker with cardiovascular disease. Industry classifies work performance into four categories as follows: base, regular, premium and unsatisfactory. Not all employees are rated but where this was accomplished the findings were striking in cardiac workers. The work performance of an average plant population is about 50 per cent regular and 20 per cent premium in performance. In contrast, it was noted that 26 per cent of the cardiac workers showed premium performance in 1955, increasing to 36 per cent in 1956 and to 76 per cent in 1958. Twenty-one per cent were regular in performance and 3 per cent were base.

TABLE IV

Comparison of Absenteeism Due to Cardiovascular Disease Over a Four Year Period (Per cent of all causes)

Year	Absences (%)	Days Lost (%)	Average Time Lost Per Case (weeks)
1955	6.0	7	8.2
1956	6.3	13	8.5
1957	9.0	12	14.0
1958	10.0	17	15.0

ABSENTEEISM

In 1955, 1956 and 1958 accurate statistics were obtained concerning absenteeism in the general plant population, comparing employees with cardiovascular disease to the average (Table II). Absenteeism has been presumed to be a great risk in employment of workers with cardiovascular disease. The findings represent the same basic groups in this study and are probably significant.

It is important to note that in 1958 about 84 per cent of the group with arteriosclerotic heart disease lost only an average of 8.7 days; 80 per cent of the group with rheumatic heart disease averaged 6.7 days lost; 80 per cent of the group with hypertensive heart disease group lost an average of five days and 90 per cent of the group with essential hypertension lost an average of 8.4 days per year. These figures compare favorably with those on the average plant employee.

In comparing absenteeism due to all disease causes with that due to cardiovascular disease it appeared that workers with cardiovascular disease compared favorably with other groups (Table III).

Workers with cardiovascular disease appear to have a good record in terms of absenteeism, but cardiovascular disease is as a rule, progressive and the problem is likely to increase with the passage of time. We find as the years pass that the total absenteeism, per cent of absences, per cent of days lost and average time lost per case are increasing (Table IV). Although absenteeism due to cardiovascular disease is increasing gradually it should be noted that over the eight year study period it was fifth as a cause of absenteeism (percentage of absences) in the Gillette population.

Although employers are concerned about compensation losses and medical and sickness benefits, our study indicates that management is not loading its insurance risk when rehiring persons with cardiovascular disease.

Comments

In this study of employees with cardiovascular disease we were able to demonstrate that with proper job placement and careful long-term follow-up this group of employees performs well and does not constitute an undue risk to the employer. We found no evidence that continued employment or return to work caused an aggravation of the underlying cardiovascular disease. It is of interest that although individual workers' physical capacity was often reduced as a result of cardiovascular disease there was seldom a reduction in capacity to perform his jobs. This experience confirms that of others[2] that most jobs in industry do not require large energy expenditure and are within the physical capacity of most cardiac patients.

In our study we were able to answer in part some of the questions we asked from the standpoint of the employer. We noted that employees with cardiovascular disease did not endanger other employees; they were able to produce at a profit; their value to the employer was great, but we did not attempt an answer to the question on possible increased insurance risk because of the relatively small number of employees involved in our study; the decision to rehire apparently had a salutary effect on the other employees and we found no evidence that it altered the seniority system in the plant. Although there is ample evidence to support the thesis that the person with cardiovascular disease is an effective employee and does not cause undue risks to the employer,[2] many employers are fearful of the possible risks. The present workmen's compensation laws are considered to be an increasingly important deterrent to the hiring of persons with cardiovascular disease because of the liberal interpretation of the laws and the classification of many degenerative cardiovascular diseases as industrial accidents. Unless changes are made the problem will become increasingly difficult and ultimately not only the patient but also the whole community will suffer.

From the standpoint of the practicing physician the lesson to be learned from this study is that the great majority of persons with cardiovascular disease who have been employed and have clinical evidence of disease can either continue working or can return to work after a period of disability. They can work profitably without harm to others or themselves for long periods and they are certainly happier than if retired unnecessarily.

Summary

A group of 219 industrial employees with cardiovascular disease has been observed over an eight year period.

Employment has not been associated with an increased mortality, excessive absenteeism or apparent increase in insurance risk. The employees with cardiovascular disease have been loyal employees and have had an average performance above that of the plant population as a whole.

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Returning the Farmer with Cardiac Disease to Work*

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THE FARMER with cardiac disease presents some unusual problems differing from those of the factory worker with cardiac disease. The farmer is not only self-employed but also involved in heavy physical work under a wide range of environmental conditions; the scope of his work is generally not understood. In this paper the nature of farm work and certain social differences observed in the farm worker are discussed; the work and environmental stresses are explained and methods for their reduction are suggested. This material together with information on agencies that can help the farmer is presented to aid the physician in the rehabilitation of the farmer with cardiac disease.

THE JOB

Farming and industrial work differ in several important respects. The farm operator is usually at once capitalist, manager and a substantial part of the labor force of the business. The capital investment per worker on a Midwestern hog and corn farm may be as high as $50,000 per worker. In this geographic area the average size of the labor force has been one and a half to two full time workers per farm for the last two decades.

The typical farm is a family unit employing the farmer and one or more sons; the housewife may help in the fields until the children are old enough to take her place and perhaps after the children have left the farm. Seventy-four per cent of all farms in the United States employ only family labor. This type of family business represents a unique way of life from a social and psychologic point of view. Consequently, heart disease poses a peculiar kind of threat to the farmer which, in turn, creates special problems for the physician who would rehabilitate him.

Important differences between farmers and industrial workers are shown in Table I. In the performance of his job, the farmer must take into account market conditions, capital resources, the vicissitudes of the weather, community attitudes and the opinions of other family members who are also actively engaged in the same enterprise.

The concept of the large farmer working like a city businessman is more imaginary than real. In 1954, the last year for which data are available, only 2.8 per cent of farms in the United States sold more than $25,000 worth of products. An even smaller number, 1.1 per cent, relied exclusively on hired labor. However, there is a slow but steady trend toward larger farms, with some of the smaller farms going out of business, without increasing the labor force per farm.

The total labor force involved in agriculture is decreasing with the decrease in the total number of farms. In 1954 there were 4.1 million farm operators, 2.7 million unpaid family members working fifteen hours or more a week on the farm and only 0.7 million regular hired workers and paid family workers. This provides an average labor force of 1.8 persons per United States farm. On the other hand, some of the work that was formerly done by the farm labor is now done by specialists from the town.

There is a large seasonal labor force, 3.5 million in 1959. This is probably an underestimate as it does not include all laborers employed by packing houses to harvest crops on farms.

* The material in this paper is based upon the results of the Purdue Farm Cardiac Project. This research has been supported by Purdue University, Lafayette, Indiana, and Northwest Indiana Heart Associations; National Institutes of Health (H 3185) and the American Heart Association.

TABLE I
Differences Between Farmers and Factory Workers

Farmer	Assembly-line Worker
Self-employed.	Works for others.
Provides the capital, the management and about half the labor force.	Capital provided by stockholders, management decisions made by specialists, labor force larger and much more specialized.
Works variable hours; sets own work pace.	Works relatively constant number of hours. Does not set own pace.
Works at home. Family involved in the job.	Place of employment and home separate; therefore, the family not directly involved in the job.
Works under scrutiny of the community.	Observed by fellow workers and supervisors but more insulated from community.
Works out-of-doors subject to both the stresses of the environment and the uncertainties of the climate.	Physical environment usually controlled.
The job has a cultural tradition including both scientific and folk attitudes toward work methods and the meaning of work.	Newer and more specialized jobs may have less traditional elements.
Performs a more complete operation involving knowledge of mechanics, agronomy, animal husbandry, finance and management.	More likely to perform a partial operation involving a narrower range of skills.
Identification with the job and the final product.	Less psychologic identification with the job and final product.

Industrial workers frequently engage in more strenuous activities off the job or in commuting than they do at work. On the other hand, the farmer's work activities are often strenuous even today and his leisure activities are usually relatively low in energy demands. Therefore, in evaluating the physical activity of the farmer the leisure activities, except hunting, generally need not be considered in detail.

The labor requirement of the farm operation is seasonal; peaks of activity represent the work of planting and the harvesting of grain and hay. The duration and intensity of the daily work involved in tending livestock are also variable, being highest when the cows are calving or the sows having their litters. Many farmers keep no livestock and there may be practically no work to be done in the winter; when spring arrives these farmers are projected from idleness into the intense activity of preparing the land and planting the seed.

The farmer works in a highly variable environment; he is exposed to extremes of cold in the winter and extremes of heat in the summer. The hot, humid climate which is good for the growth of corn, the major feed grain in agriculture in the United States, necessitates a high heat stress which is increased by the heat from the tractor engine.

Despite subsidies and crop support programs the farmer's economic status is uncertain. Price fluctuations, unexpected weather conditions, pests and diseases make farm income less stable than industrial income; however, in the long run the farmer who owns his own land has job security provided he is able to keep solvent.

The job of the seasonal worker is almost entirely manual; in some areas he is employed mainly in harvesting vegetable and fruit crops. In this case, the worker will be a member of a gang moving from farm to farm. He is generally paid on a piece rate basis. In other cases, the workers stay on one farm for a season doing a sequence of jobs from hand hoeing and weeding crops to harvesting.

The wage rates earned by seasonal farm workers are low, $0.50 to $1.20 an hour. Workers with large families frequently receive more money when they are unemployed and on "welfare" than when working.

THE MAN

In returning the farmer to his work there are certain factors apart from the job to be kept in mind. Some attitudes toward health and the medical profession have operated against the successful rehabilitation of the farmer with cardiac disease. The following beliefs were

TABLE II
Sources of "Information" Received by Farmers with Heart Disease*

Information	Source		
	Doctor	Family	Friends
You can have a long life with heart disease	65†	24	41
Quitting work or retiring shortens your life	8	15	61
You should follow your doctor's advice better	6	39	14
You'll never work like you used to	44	26	35

* From: RIEDEL, D. C., EICHHORN, R. L. and MORRIS, W. H. M. Proceedings of the Purdue Farm Cardiac Seminar.[1]

† Figures represent per cent of cases reporting statement by source. Percentages reported are based on the 203 respondents to whom this portion of the questionnaire was submitted.

held by a group of 362 farmers surveyed in central Indiana in 1956:

If you wait long enough you can get over most any illness..... 33%
A man can't afford to call a doctor these days..... 13%
I'd rather be sick than go the to hospital... 20%
Some of the old-fashioned remedies are better than the things you get at the drug-store..... 39%

The farmer with cardiac disease who distrusts doctors or hospitals, believes he cannot afford a doctor or tries to treat himself will not get the care he needs. Such mildly antimedical beliefs are also a real obstacle to the physician attempting to help the farmer return to a normal life. In each case, farmers who subscribed to these beliefs were less likely to comply with their physicians' therapeutic advice.

Farmers have often been characterized as being compulsive about work. Hard work is regarded as virtuous and an end in itself despite its economic indefensibility. Indeed, the farmer of today makes more money with his brain than with his muscles. Sheer hard work is not usually associated with high farm income. This attitude toward work is often related to the rejection of modern labor-saving technics and the retention of obsolescent and uneconomic farm practices.

Attitudes Toward Suggested Changes in Work Habits: A farmer's compulsiveness toward work may also prevent him from complying with the physician's advice, especially if the therapeutic prescription suggests changes in behavior while working. A substantial number of farmers (more than 50 per cent of those surveyed) endorsed the following beliefs: quitting work or retiring shortens your life; the worst part of being sick is that the work doesn't get done; even if I were financially able, I couldn't stop working. Farmers who agreed that these statements reflected their own opinions were less likely to follow their physician's instructions. Over 90 per cent of the respondents suffering from heart disease remembered being told to change their pattern of work in some way. Those who did comply reported that their doctor's prescription for work was hard to follow because it upset habitual practices. But, nearly 15 per cent reported that they did less than their physician suggested and 4 per cent reported that they did nothing the physician ordered.

Where Farmers Get Their Information: The response of a person to any severe illness such as heart disease is dependent upon his information and beliefs about his disease. It is, therefore, important that the patient be well and correctly informed about major diseases. Information sources range from advice given by physicians, previous experience with other illnesses and the experience of friends and relatives who have had the particular illness, to the patient's general ideas on the maintenance of health, reducing the pace of work, retiring, death and the like.

The differences in content between the various sources of information are interesting. For example, few physicians suggested that quitting work would shorten the farmer's life; however, this belief was widely held in the community and passed on to the farmer by well-intentioned friends and neighbors (Table II).

The responsibility of the physician in public health education is emphasized by reliance of the major portion of farmers surveyed on their family physician for information on heart disease.

PROBLEMS IN PRESCRIPTION FOR WORK

The underlying problems in management of the cardiac patient apply to the farmer and nonfarmer alike. The difference becomes apparent in getting the farmer to the physician, in the effect of the absence of the farmer from his business, especially in the case of acute

conditions, and in the development of a prescription for work.

Acute illness of the farmer presents some problems that do not occur to the same extent in urban populations. The sick farmer will feel a need to complete his day's work if this is physically possible. However, if his family and neighbors know his situation, help in completing work is usually available. Once the farmer has decided to seek medical attention it may take some time before he can obtain it. In central Indiana, with comparatively densely populated rural areas, a third of the farmers reported that they lived ten or more miles from their physician.

Medical services in rural areas lag behind those in the cities. In some counties there are no internists. Hospital and laboratory facilities are generally available within the county but many patients are moved into a hospital out of the county to obtain the services of an internist. Hospitalization at some distance from the community may lead to a sense of personal isolation. Anxiety about the business on the farm may then be intensified.

From the moment the farmer first has an acute episode of heart disease, his inability to contribute to the farm labor supply is felt. If the episode occurs during a slack season the effect may be small. In a busy season the effect will be serious and may almost be disastrous. If necessary, the family must obtain assistance through the help of neighbors, a farm organization such as the Farm Bureau or the Grange or through the Agricultural Extension Service. Friends and neighbors are usually ready and able to help if they are aware of the needs. The patient must be assured that his farm is being cared for, that his livestock are being tended and that he will not be faced with a wrecked farm operation on his return home.

To the farmer with cardiac disease the prospect of seeking a new occupation is very discouraging; he is, on the average, seven years older than his city brother when he suffers the first episode of arteriosclerotic heart disease and, above all, farming is not only a livelihood but also a way of life for him and his family. However, the farmer does have a wide range of alternatives permitting him to stay in his occupation; these are discussed later. He will usually worry until reassured by his physician that there is a future for him when he returns to the farm.

Once he has returned home it may be difficult to restrict his activities. Specific instructions on what he can and cannot do are necessary. However, the instruction must be practical to encourage compliance.

Throughout the federal government a federal-state system of agricultural extension has been established. This is organized from the state agricultural colleges and is represented in most counties by a County Agricultural Agent or Advisor and his staff. These officials provide a free service for farmers. The farmer with cardiac disease should be advised to seek help from the agricultural extension service in adjusting the farm operation to his impaired capacity.

The Stresses of Farm Work

PHYSICAL STRESSES

The physical stresses of the farmer result from three basic types of work as follows: (1) *positive work*, applying a force to move something, for example lifting or pulling a lever; (2) *static work*, applying a force to support something, for example holding a load, pushing to open a barn door; (3) *negative work*, applying a force to restrain something, for example setting down a load. These types of work cause different changes in the metabolic rate and the heart rate. Static work, although often moderate in energy cost, increases the pulse rate more per unit increase of energy than do the other types of work. Therefore, the static content of the job should be kept to a minimum to reduce the over-all work stress.

In performing static work, the blood flow to the working muscles is impeded by maintaining the muscles in contraction; in the dynamic positive and negative work, alternate relaxation and contraction of the muscles stimulate the blood flow. This explanation is proposed by Lehmann[2] for the difference in heart rate changes between static and dynamic work.

Another major effect on the cardiovascular system of physical work is the relationship of work to the intrathoracic pressure. Physicians have long recognized the cardiovascular response caused by straining at stool.[3] This increases the intrathoracic pressure causing changes in the cardiovascular dynamics similar to those involved in the Valsalva maneuver. Certain work activities such as lifting heavy weights and swinging an ax or a heavy hammer result in a similar type of cardiovascular stress

but at lower levels. These activities cause more distress to the patient with cardiac disease than would be expected from energy cost.

Peak Stresses: The average stresses of farm work although appreciably higher than those in industrial work are generally moderate, perhaps three to three and a half times the resting rate. However, the peak stresses may be as high as eight to ten times that of resting; it is these peak stresses that are likely to trouble the cardiac patient. Peak stresses are associated with activities such as lifting or carrying heavy loads, sacks or bales; carrying even light loads over heavy clay soil or in deep snow; climbing up machinery, ladders or stairs; running or chasing livestock; holding livestock, for example, for castrating or putting a ring in the nose; pulling or pushing heavy loads such as feed carts or heavy barn doors. These stresses are mainly associated with work with livestock or "chore work."

Certain activities using a farm tractor also involve relatively high energy expenditure, for example, plowing and using a loader mounted on the front of the tractor. Attaching machinery to the tractor may involve pulling or lifting very heavy weights. At corn planting time, in addition to driving the tractor, a large amount of fertilizer is handled. This comes in 50, 80 or 100 pound bags. In a day as much as $3^1/_2$ tons may be handled, most of it twice, when loaded out of storage and when placed in the fertilizer boxes on the planter.

In addition to high work stresses, the farmer works very long hours at certain seasons of the year; for example, at corn planting time over 70 per cent of the farmers in the Purdue Farm Cardiac Survey sample reported working twelve or more hours on an average day.

Reducing Physical Stresses of Farm Work: Most if not all of the major physical stresses in farm work can be reduced and many can be eliminated. Some tasks such as shoveling have "built-in" rest periods and the farmer with heart disease may adjust the pace of work to suit his capacity. The same is true for climbing stairs or walking uphill.

Farm work simplification points the way to modifying or eliminating these heavy tasks. For example, lifting sacks can often be avoided by storing them on a platform level with the bed of the truck; a two-wheeled barrow can then be used to move the sacks, eliminating lifting.

With some additional investment much of the "chore work" can be performed mechanically. The cost of running an electric motor that performs the physical work done by an average farmer in an eight-hour day is about $0.08. A mechanical silo-unloader (costing about $1,500) and a mechanical feed bunk or a self-feeding silo would remove the hard work from feeding cattle. There is little reason to carry water on the farm today; pressure water systems are not too expensive for almost any farmer.

While milking cows, the need to stoop (at least three times per cow at each milking) can be eliminated by a two-level milking parlor, the udder of the cow then being at the same level as the worker's elbow. Carrying milk cans may be eliminated by using a pipeline and a bulk milk cooler. Keeping the cows loose in a yard, then using mechanical handling, is often an economical way of avoiding the heavy physical work of manure removal.

Automatic feeding and watering of poultry is quite common on the farm. If the farmer cannot afford an automatic feeding system, feed purchased in bulk can flow by gravity directly into a container suspended from a single rail and dispensed into the feeders. This eliminates carrying feed and reduces the distance walked.

The energy expenditure for driving the farm tractor can be reduced by *power-steering and a comfortable seat*. Power-steering reduces the peak forces that must be exerted on the steering wheel and also eliminates the transmission of steering shocks from the front wheels. A rough-riding seat causes a higher energy expenditure and a greater increase in pulse rate than a comfortable seat. The addition of power-steering and a superior seat adds relatively little ($200 to $300) to the usual cost of a modern tractor ($4,000 to $6,000). Many farmers are surprised at the reduction in fatigue by these two improvements.

The stress of handling bags of fertilizer can often be avoided by using liquid or gaseous (ammonia) fertilizer which usually costs no more or, in some areas, by handling solid fertilizer in bulk. Failing this, the stress may be reduced by handling fertilizer in smaller bags.

Apart from such changes, the farmer can also reduce the physical stress of work by taking *frequent short rest pauses*. It has been demonstrated conclusively that the over-all work stress is much more effectively reduced by many

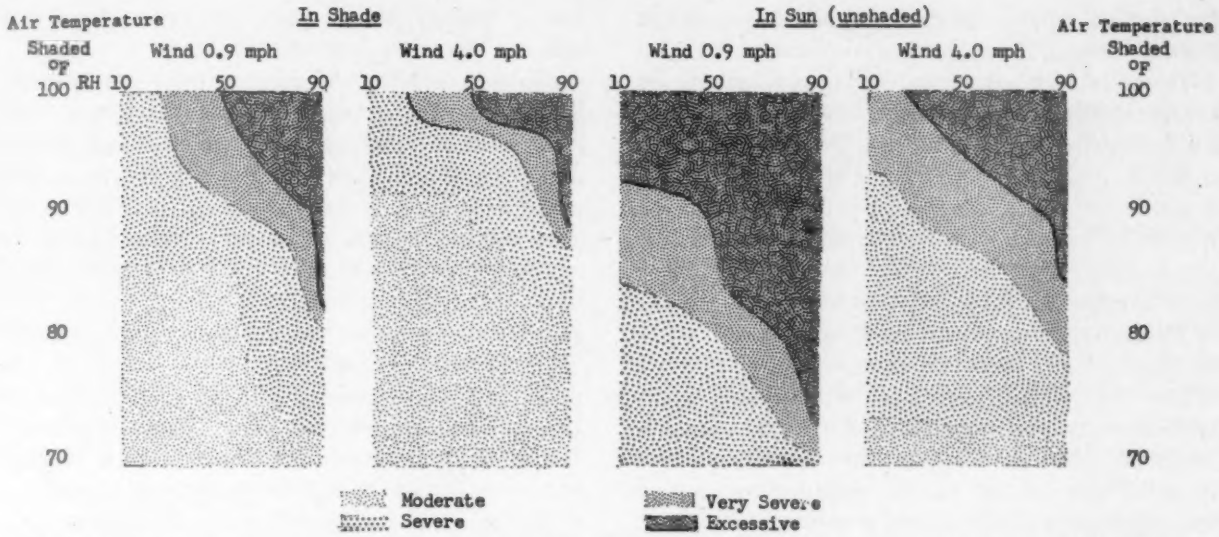

FIG. 1. Heat stress during sustained work at two and a half times resting rate (250 cal./hour). RH-relative humidity. (Data from BELDING, H. S. and RIEDESEL, M. L.[7])

short rest pauses than by the same amount of time spent in fewer but longer rest pauses.[4] A change of activity is not as good as complete rest; for example, if the farmer uses his "rest" pause to lubricate the combine when harvesting, the effect of the pause is greatly reduced.

ENVIRONMENTAL STRESS

Effects of Heat: The farmer has to do much of his work out-of-doors regardless of the weather. In the cold, working is helpful as an added source of warmth. The patient, if he is reminded of it, will recognize this from his past experience. On the other hand, in hot weather the heat produced by the work adds to the heat to be dissipated from the body; in addition, it is probable that working in hot weather involves a higher expenditure of energy than does performing the same task in moderate weather.[5] Working in the heat imposes demands on the vascular system not only to supply the working muscles but also to convey heat from the body core to the periphery. The effect of a given cardiovascular impairment on the capacity to secrete sweat is not known.

Recent work by Sancetta[6] on the hemodynamic effect of exposure to dry and warm environments (98°F. and 40 per cent relative humidity) reveals a significant decrease in the pressure in the pulmonary artery and the aorta. This reduction in pressure, apparently a result of general vasodilatation, leads to a decrease in coronary blood flow. Thus, apart from inability to maintain thermal balance, the patient with cardiac disease may also suffer from coronary insufficiency when exposed to considerable heat stress.

Measures to Reduce Heat Stress: The heat load on the man is the sum of the metabolic and radiant load; above 95°F. the convective and conductive load out-of-doors will be positive but negligible. The total load can be reduced by reducing the metabolic component by using power-steering on the tractor, or by reducing the radiant component by using a sunshade. Sunshades are available at low cost for all models of tractors.

The evaporative losses can be increased to some extent by using a fan. However, to obtain a substantial improvement the air speed may be high which may cause discomfort or increase the rate of evaporation above that which can safely be sustained by the man. Air-conditioning, which is in production for some farm machinery (grain combines and tractors), increases both the evaporative and the convective heat loss; it is generally accompanied by shading, which reduces the radiant heat load.

Heat stress can also be reduced by frequent short *rest periods taken in the shade.* Once the body core temperature has risen one or more degrees (Fahrenheit) a prolonged rest pause is necessary to dissipate the heat. If short rest pauses are taken in the shade, a high peripheral blood flow is maintained and the evaporation of sweat continues. However, in longer rest pauses the stimulus to sweat may be decreased, reducing the rate of recovery. The farmer used to rest his horses in the shade on the headland of the field; in this way he also took a rest

for himself. Since he does not need to rest the tractor, he usually neglects resting himself.

It may be possible for the physician to be quite specific in his advice to his cardiac patient on heat stresses. Although the heat load is difficult to assess precisely, Figure 1 provides a guide for estimating the heat stress at given metabolic rates at two wind speeds, both in the shade and in the sun, using the dry bulb temperature and the relative humidity.[7]

Heat stress indices of up to 30 are considered to be moderate. Indices between 40 and 60 are severe for healthy persons, necessitating some reduction in the physical work load. Indices between 70 and 90 are very severe. Only a small percentage of the population can be expected to maintain even a moderate level of physical activity (in the range of two and a half to three times the resting metabolic rate) when the index is over 70. An index of 100 is the maximum strain that can be tolerated by healthy, acclimatized, young men for an eight-hour exposure. The effect of shade and wind are clearly revealed by comparing the heat stress index at the same temperature and relative humidity but with different wind speed, or shaded versus unshaded (Fig. 1).

Heat Injury: It should be remembered that acclimatization is an important factor in the prevention of heat injury but does not provide immunity. The farmer with cardiac disease should be warned of the danger from heat early in the summer.

Obesity is clearly associated with susceptibility to heat injury;[8] the increase in the probability of injury in an obese man can easily be ten times that of subject of normal weight. This is another reason to attempt to bring the weight of the farmer with cardiac disease within the normal weight range.

Hygienic Precautions to Reduce the Effect of Heat: Suitable clothing and hat. In the direct sun, protection is needed against the ultraviolet rays which cause sunburn and sunstroke. The clothing should be moderately thick and light-colored to reflect the radiation. The clothing should be loose-fitting and permeable, so that sweat can evaporate through it. Under a shade the clothing should be lighter in weight; the color is relatively unimportant because most of the radiation is stopped by the shade.

In the direct sun the ideal hat is an aluminum-lined sunhelmet of light color with space for air to circulate between the head and the lining. In the shade, no hat or a peaked cap fitting loosely with space between the head and the top of the hat is satisfactory.

Drinking habits. A healthy man can secrete 8 L. of sweat in eight hours; therefore, it is important to advise the farmer to drink plenty of water when working in hot weather. The sodium–potassium balance must be observed. The farmer if not on a salt-restricted diet is normally advised to take extra salt on the food or a trace of salt in the water, about 1 teaspoonful per gallon, which is not enough to taste. The physician may also find it necessary to increase the level of salt intake of a farmer on a low-sodium diet working in a hot environment. Eating fresh fruit and drinking plenty of fruit juices also helps the sodium–potassium balance.

Eating habits. On hot days eating a light midday meal of foods with a high moisture content is helpful to the water balance. Cakes, breads and starchy food require more water for digestion. Heavy meals of food of high specific dynamic action add appreciably to the heat load by the heat produced by the work of digestion. The diversion of blood flow to the portal circulation following a heavy meal reduces the effective blood flow to the skin; the vagal reflex stimulated by the distended intestinal tract tends to slow the circulation; thus, the ability to respond to heat is impaired.

Effect of Cold Weather: Cold weather does not add appreciably to the stress of a healthy man at work if he is suitably clothed. The weight and bulkiness of the clothing and boots may increase the energy cost of work. The association of anginal pain and exertion in the cold in people with arteriosclerotic heart disease is well established although the mechanism is not clearly understood. Farmers with this disease should be warned of this and other stresses connected with cold weather, for example, walking in heavy snow or shoveling snow.

The farmer doing the chore work finds it difficult to keep warm during a rest pause in very cold weather. He will not want to come back to the house to rest in the warmth, so he might be advised to have a warm area in the buildings in which he can rest.

In modern farming there is a tendency to keep animals in confinement, especially in winter. It is often possible to construct a shelter so that the farmer is protected from the wind and does not walk through the snow as he goes out to his stock in the buildings and yards on cold, snowy days.

EMOTIONAL STRESSES

Since the load on the heart muscle is proportional to the product of the heart rate times the systolic blood pressure,[9] it is clear that emotional stresses add to the total cardiovascular stress. However, their quantitative effect remains indeterminate. The stress of a surgeon, a man working under considerable tension, has been estimated to be over four and a half times that of a heavy industrial worker such as a steel mill operative.[10] On the farm the additive effect of stresses is perhaps best illustrated by chasing hogs on a hot day: the work stress is high, the heat stress is high, and no farmer chases hogs without considerable emotional stress.

Although the results of emotional stress cannot be measured like the heart rate or temperature, their magnitude must be recognized. The subject knows when his emotional tensions rise substantially and remembers the feeling of exhaustion after undergoing severe emotional stress. The physician can, by careful discussion, identify the typical causes in each patient.

The nature of the stress can be explained and the cardiac advised that many of these stresses can be eliminated or reduced. Activities beyond his physical capacity, for example, pushing a car that is stuck in the snow, must never be attempted. The high work stress and failure leading to frustration will then be avoided.

The risk of farming together with the risk of emotional tensions may be reduced. For example, the acreage of corn that the farmer with cardiac disease intends to plant must be based on a larger margin of safety than is necessary for the "well" farmer. The risk of anxiety, of getting the crop planted, of long hours necessary if the farmer gets behind schedule will then be minimized. Other risks may be reduced by insurance. For example, hail may wipe out a whole crop; for a small premium the farmer may obtain crop insurance and so reduce the risk of loss and the risk of emotional tension.

Good farm records will facilitate preparation and, if necessary, substantiation of tax returns. Some farmers find getting this kind of work done more difficult than doing their field work. Competent assistance can reduce stress from this cause.

Uncertainty and lack of knowledge also cause emotional tensions for the farmer when he has to make decisions. There is a great deal of information available to the farmer through the extension service, the farm press, radio and television; a well informed farmer can reach a logical decision on most farm problems without worrying.

Problems in Farm Management for a Farm Operator with Cardiac Disease

Problems in farm management for the cardiac patient who operates a farm will generally be outside the usual area in which the physician wishes to give advice. However, it is important that the farmer receive assistance in adjusting his farm activities to his functional capacity. The physician can often help by referring his patient to the facilities available through the agricultural extension service. Since some farmers with cardiac disease would find a better opportunity in employment off the farm, the vocational counseling service available to all through the State Department of Vocational Rehabilitation is also often useful in rehabilitation.

The farm operator is faced with making two basic types of decisions as follows: (1) "what to do" (e.g. what to grow, what livestock to keep), and (2) "how to do it" (e.g. system of management, work methods, mechanization).

"*What to do*" *Decisions:* The first decision to be made by the farmer struck by heart disease probably is whether to continue farming. He may have farmed for most of his life, often earning a surprisingly small income for his relatively high capital investment and his hard work. This decision must, of course, be left to the farmer. However, he should be appraised of the alternatives which might include taking a full or part-time job off the farm, perhaps associated with agriculture; retiring or buying some other business; or, most commonly, adapting the farm operation to his changed situation. He may do this by replacing his loss in working capacity by family or hired labor, by capital invested in machinery or by reducing the scope of the farm operation to fit his impaired capacity. The responses of a group of forty-four farmers who had had myocardial infarction (Table III) illustrate all of these possibilities.

The family often provided the additional labor to enable the farmer with cardiac disease to continue farming. This commonly occurs with natural aging as well as with disease. Sometimes the farm operation was reduced

TABLE III
Major Changes in the Farm Business and Labor Force of Forty-Four Patients with Myocardial Infarct

Change	No.
Farm substantially unaltered	16
Children and/or wife help	11
Hired more labor	3
Labor force unaltered	2
Reduced livestock*	10
Children and/or wife help	5
Hired more labor	3
Labor force unaltered	2†
Reduced crop land‡	7§
Children help‖	3
Hired more labor (summer)	1
Labor force unaltered¶	3
Rented land to others	9
To sons; farmer "fills in"	1
Farmer took nonfarm job	3
Kept some stock	3
Farmer retired	2
Quit business	4
Sons took over	3
Unstated reason	1

* Three dairy herds sold.
† One farmer also works as County Assessor.
‡ Excludes Soil Bank, mentioned by one farmer.
§ Two included in this group of seven also reduced livestock and are also counted in preceding group of ten.
‖ Two also reduced stock.
¶ One also reduced stock.

until a son was old enough to enable the original operation to be restored.

Only farmers with good managerial ability can afford to hire an extra full-time worker. In the Midwest this would cost $4,000 to $5,000 in wages, housing and perquisites. A considerable expansion of the business would be necessary for the farmer to retain his former level of income with this added expenditure. However, in rural areas it is still usually possible to hire labor to help during the peak seasons of planting and harvesting. This part-time labor is usually a much cheaper alternative and more practical for the farmer who cannot get the extra help from his family.

It is often preferable for the physician to advise a small steady work load rather than suggest that the farmer retire at once and completely. Here again, the county extension agent can help the farmer to evaluate the alternatives within the prescription of the physician.

After the labor resources of the farm are established, farm management specialists may help the farmer to plan the cropping for the land within the labor supply. If the labor supply has not been increased to compensate for the impairment of the farmer the acreage of crops may be reduced. This may be done by changing the cropping system, by giving up land that is rented or by renting some of the land for a share of the crops produced by the tenant.

After planning the crops the livestock enterprises are planned to use up the rest of the available labor. The enterprises already on the farm may be changed in size or an enterprise requiring less labor substituted for one with a high labor requirement; for example, beef cattle substituted for milk production. The changes in crops and livestock may greatly affect the income of the farmer.

In the most severe cases, the farmer may be advised to rent out all of the farm, perhaps keeping a few livestock as "busy work." If the farmer has been contributing to social security and is of retirement age he may be able to obtain an adequate income from renting the farm and receiving social security benefits. In a few cases the farmer will leave the farm, handing it over to some member of his family or selling the business outright.

The number of farmers in the United States is decreasing annually and many of those still on farms, either as farm operators or farm workers, could earn more money off the farm; nevertheless, it is usually difficult to persuade even healthy men to leave the farm. The farmer with cardiac disease may be able to get employment in some agricultural business or in a local government office for which he is qualified. For example, some farmers with heart disease have taken jobs as salesmen of agricultural seeds, fertilizers or feeds, salesmen of insurance to farmers, county assessors, crop recorders and so on.

"*How to do it*" *Decisions:* The "how to do it" decisions are little, if any, less important than the "what to do" decisions. Decisions in this area can greatly reduce the peak and average levels of energy expenditure.

It is in this area of "how to do it" that the farmer with cardiac disease has the best opportunity to compensate for his impairment and has the greatest need for advice. This advice is readily available through the county agricultural agent and the state extension specialists.

The farmer with cardiac disease may substitute capital for his labor. Equipment can be

purchased to do much of the "chore" work automatically. The farmer may admit, after being forced by infirmity to make the changes, that these changes should have been made years ago.

Sources of credit are usually available to permit mechanization of the farm over a period of years. The sources include the Agricultural Stabilization and Conservation Program (crop loans and soil bank and conservation payments) and the Farmers Home Administration (improvement loans), as well as sources available to nonfarm businesses. The Vocational Rehabilitation Service has also been known to contribute to the cost of labor-saving devices for the impaired farmer. However, a sudden need for complete mechanization may present problems particularly if the lending agency has doubts about the life expectancy of the farmer.

A program of education in work simplification is helpful to farmers making "how to do it" decisions by provision of technics which the farmer can use to evaluate his own work methods. A similar program on work simplification in the home has been successful in helping the homemaker with cardiac disease.

Sociologic Implications for Rehabilitation

A farmer who has had an episode of cardiac disease may have great difficulty in readjusting his enterprises to reduce his work load. His capital is tied up in his farm and his skills are not easily transferred to other kinds of employment; however, it has already been demonstrated that many alternatives exist for him.

Since farming is more than an economic undertaking and is a way of life, the successful rehabilitation of the farmer with cardiac disease must take into account the farmer's attitudes toward health and the meaning that work will have for him. A farmer cannot abruptly cease hard satisfying work that brings in real results (a crop) without psychologic consequences. Physicians must remember that vague suggestions to "slow down" have little chance of being accepted when they run contrary to habitual work practices which have been followed for decades. Instructions need to be specific and workable.

The farmer may have to be prepared to accept a lower standard of performance as a result of his heart disease; he may not get the crops in so early or there may be a few weeds in the fence. He should be counseled that his neighbors, who notice such things in judging a man, will usually make allowances. In any case, he must use his limited physical resources on essentials, not frills.

The farm family is also involved in the adjustment of the head of the household to a reduced work load. Some families have sons who can assume the responsibilities their fathers carried; other families do not. Some wives are willing to change their own habits in deference to their husband's needs; others are not. The physician may need to counsel the whole family in an effort to elicit its help.

Finally, neighbors can assist in the rehabilitation of the cardiac-impaired farmer or frustrate his adjustment. Neighbors can help harvest a crop, thus sparing a recently stricken farmer an additional worry. An irresponsible comment such as "you should quit work before you kill yourself" can undo months of careful education on the part of the physician trying to help the farmer return to his job. Criticism of the impaired farmer for not doing unessential jobs is also harmful to rehabilitation. It would appear, then, that the physician must also actively engage in community education attempting to raise the level of public understanding of heart disease and its relationship to work.

The Role of the Agricultural Work Classification Unit

In the same way as the work classification unit plays a part in the rehabilitation of the industrial worker with cardiac disease and in physician education, a demonstration in Iowa has shown that an agricultural work classification unit is feasible.[11] In this case the rehabilitation team consists of a physician, a vocational counsellor and a county agricultural agent. Farmers have also been through the industrial work classification units but the regular staff of the unit is rarely able to help with problems of farm management.

There is some reluctance on the part of physicians in rural areas to refer patients to specialists. One major problem in setting up a work classification unit in a rural area, as in an urban area, is to obtain a satisfactory case load from the physicians. It remains to be seen whether this is possible.

The approach being taken in the farm cardiac research program in Indiana is that the work classification unit has not proved practical for the rehabilitation of the vast majority of patients with cardiac disease. Less than 1 per

cent of the cardiac patients in the nation have been through a unit. On the other hand, most cardiac patients receive assistance mainly from the family physician. He, or the specialist to whom he may refer, evaluates the farmer with cardiac disease and could and should also refer for nonmedical assistance to the people who would comprise the agricultural work classification unit. Research has not yet reached the phase that would demonstrate the feasibility of this concept; however, it is evident that in the forseeable future, more can be done for the farmer with cardiac disease by education of physicians than by the establishment of work classification units.

Summary

Farming as an occupation still requires much physical work although today the drudgery is neither necessary nor remunerative. The requirement of hard work acts as a selecting factor, discouraging the unfit from entering the vocation.

The activity of farming appears to have a prophylactic effect on the manifestation of coronary heart disease. However, the nature of the farm business makes the impairment of the farmer in the acute stages of heart disease a serious threat not only to the man but also to the future of the business.

The farmer commonly owns all or part of his farm; he has many alternatives which permit him to live usefully with his heart disease. These alternatives range from changing work methods, the size of business being unaltered, through obtaining more labor to retiring.

The complexity of the alternatives makes decision-making difficult. However, once the acute stages of the disease are overcome, the farmer may obtain help in planning his farm from the agricultural extension service; there are also sources of credit which can provide capital for mechanization to aid in overcoming the physical impairment.

The physician has a real opportunity in rehabilitation of this highly motivated group of patients. Apart from his medical skills, the physician's success will depend upon some understanding of the stresses of farm work and means for their reduction. The instructions to the farmer in the area of work must be specific. Compliance will often be better if the family is well informed.

Acceptance by the community of the fact that most farmers with cardiac disease are able to work within limits is essential to satisfactory rehabilitation. Most people consider the physician as the main source of information in this area. Therefore, community education on health and disease is another responsibility of the physician trying to rehabilitate cardiac patients who are farmers.

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Prognosis for Rehabilitation of the Older Adult and the Aged Hemiplegic Patient*

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THE GROWING NEED for and interest in the long range treatment of the patient who has suffered a cerebral vascular accident resulting in hemiplegia make it imperative to review the factors essential in formulating a prognosis for recovery and successful rehabilitation. In this context the term rehabilitation can best be defined as the patient's ability to use and the actual use of his remaining functions to become as independent as possible. By necessity this review is based mainly on my clinical impressions and personal experience.[1] Statistically founded prognostic information in this area is only slowly forthcoming and thus far is of limited value. Some prognostic data from several statistically controlled studies have recently become available.[2-4]

The elderly hemiplegic patient is justly considered less apt to profit adequately from the short term rehabilitation programs that are available in some general hospitals. The expense of a prolonged treatment program is therefore often considered only when adequate results may be expected. We are concerned here with an age group in which conventional vocational rehabilitation may not be expected in most instances. On the other hand, the patient's ability to care for himself, to walk and to be independent at home has become a well accepted goal. Often the fact that the care of a partially dependent disabled person at home is expected to be made physically, economically and socially easier for the family may in itself be an adequate reason for a prolonged program of rehabilitation treatment. Similar factors should be considered if the patient's eventual placement in a nursing or boarding home has to be contemplated.

Rates of immediate survival following a cerebral vascular accident are not presented here. However, it is worth while to point out that death from a single cerebral vascular accident should not be expected beyond the first two weeks after the stroke, unless there are good reasons to believe that the focus of the cerebral vascular accident itself is expanding or that a coexisting serious disease is progressing.

CLINICAL PROGNOSTIC FACTORS IN CEREBROVASCULAR ACCIDENTS

The evaluation of the cardiovascular status is paramount in predicting the outcome of the physical treatment of the disabled. Advanced hypertensive encephalopathy by itself carries a poor medical prognosis. A comparatively mild hemiparesis in a patient with moderate hypertensive encephalopathy may often result in a very unstable gait or even in the patient's inability to learn to walk at all. A multiplicity of small cerebral lesions seems to be the etiologic factor responsible for this locomotor disablement. Some patients with auricular fibrillation are able to muster enough energy to learn to walk again only after the fibrillation has been successfully converted to a regular sinus rhythm. A recent myocardial infarct overshadows all other prognostic considerations arising from a superimposed cerebral vascular accident.

Prolonged bowel incontinence is the most important prognostic symptom in a patient with a recent cerebral vascular accident. It is doubtful that there will be any essential improvement in the status of self care of an elderly hemiplegic patient who is still incontinent of bowels three to four weeks after the stroke, even with the best management and prolonged training. This statement is qualified by the provision that it does not include those patients who suffer a superimposed disease which is the

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cause of bowel incontinence and could reasonably be expected to respond to treatment. In making a differential diagnosis the common situation of fecal impaction with "overflow" diarrhea-like bowel incontinence must be excluded (by digital rectal examination) before the pessimistic diagnosis of bowel incontinence due to brain damage is decreed.

Urinary incontinence,[5] in contradistinction, has no major predictive value. It may be iatrogenically induced, as for instance due to unnecessarily prolonged indwelling catheter management, or may be a consequence of inadequate nursing care. Many hemiplegic patients stop being incontinent of urine when they learn to walk independently to the bathroom. A victim of cerebral stroke who has learned to ambulate and is not bowel incontinent but who does have inadequate urinary control must have a thorough genitourinary investigation to exclude urinary tract disease. Frequently, pathologic conditions which have been previously well compensated become evident following the cerebral vascular accident as a result of the individual's decreased ability to compensate for the preexisting abnormality.

Flexion contracture of the hemiplegic knee is the second most important prognostic factor for rehabilitation. Occasionally, mild flexion contractures (up to 15 degrees) do not progress, and although they make walking clumsy, they do not prevent it. In the older age group the average knee flexion contracture makes ambulation impossible. Motor denervation of the involved lower extremity followed by surgical straightening of the knee and ambulation training with a long leg brace is feasible in the younger age group only.

The combination of a marked knee flexion contracture on the hemiplegic side and a functionless upper extremity is, in a large percentage of cases, the reason for the patient's inability to learn to transfer unassisted from bed to wheelchair or from wheelchair to toilet seat. Often this limitation of functioning at the wheelchair level is not anticipated, and much valuable time is wasted in trying unsuccessfully to teach such a patient independent transfer technics.

A large percentage of knee flexion contractures in hemiplegic patients develop as a result of pain (withdrawal reflexes) in the involved lower extremity either from a pressure sore at the heel or external malleolus or from thrombophlebitis in the lower leg. Other causes of knee flexion contractures on the hemiplegic side are positioning, such as a pillow under the knee while the patient is in bed or too much sitting without an adequate opportunity to walk.

The type of motor involvement resulting from the cerebral vascular accident definitely influences the prognosis. Severely involved patients with "prolonged flaccidity," i.e., the knee is unstable and the upper extremity hangs limply, almost always learn to ambulate but they require a prolonged period of gait training. Occasionally such severely involved hemiplegic patients learn to walk independently only after they have been subjected to a "total push" ambulation program. In such a program the patient is ambulated by the therapist for two to three minutes of every ten minutes for several hours daily. Sometimes knowledge of special ambulation technics on the part of the supervising physician and his therapists is essential to secure success. Patients with cerebellar tract involvement and those with bilateral cerebral vascular accidents may not have even a fair prognosis for ambulation unless, as for the patients with "prolonged flaccidity," the therapeutic staff has had special experience with the problems.

Physicians who have had a great deal of clinical experience with elderly hemiplegic patients will be able to decide two or three weeks after the cerebral vascular accident whether neuromuscular re-education of the upper extremity is justified.

Sensory involvement in hemiplegia has a definite influence on the prognosis in that more time is needed to teach such a disabled patient independence in ambulation and activities of daily living. Although sensory involvement is important to the prognosis, I doubt whether the difference between the length of hospitalization needed for patients with sensory involvement and those without sensory involvement is so large for the average hemiplegic patient population as reported by Van Buskirk and Webster.[6] The question of the degree to which hemiplegic patients with sensory involvement differ from those without sensory involvement in their ultimate (at the end of their rehabilitation treatment) daily life performance still remains unanswered. It is my impression that basically patients with sensory involvement are usually not much more handicapped in their activities at home than the hemiplegics who

suffered only "pure" motor paresis. Much more information about the dependence of sensory loss upon higher mental functions has to be available before adequate prognostic correlations can be worked out. For instance, it may take years for a highly intelligent hemiplegic with almost full motor recovery to become aware of astereognosis in his involved hand because he may be using this hand automatically, getting the needed sensory information from eye-hand coordination or from the other hand in bimanual activities. On the other hand, another similarly highly intelligent patient may be so incapacitated by astereognosis that he will not use his involved hand at all although almost full motor recovery is present.

Hemianopia presents additional complications and risks, especially because of the patient's unawareness of the existence of loss of some portion of his visual field and because it is difficult for older brain-damaged patients to learn to take that loss into consideration when performing their normal activities. Yet, with patience on the part of the staff and an adequate opportunity to learn to walk, the hemianopic patient may eventually do fairly well in ambulation.

Pain in Hemiplegia: Pain must always be evaluated carefully. *Osteoarthritic knees* may not have bothered the patient at all prior to the stroke, but impaired motor control resulting from the cerebral vascular accident may cause the hemiplegic knee to be so painful that ambulation becomes impossible. A long leg brace, with the knee unlocked during ambulation, may give enough lateral stability and prevent an accumulation of minor traumas to the hemiplegic knee to enable the patient to walk again.

The most common local pain in the hemiplegic side is *the painful shoulder*. The routine examination should include testing for abnormal sensitivity in the hemiplegic shoulder, particularly in aphasic patients. It should be treated in this very early stage because a hemiplegic patient with a neglected painful shoulder may feel so distressed that he may object to any gait or self care training.

In a patient with central damage to the autonomic system, as demonstrated by a swollen hand, the painful shoulder is inclined to develop into a *shoulder-hand syndrome* with its deep impact on the patient's total behavior including his locomotor functioning. I have been impressed by the value of suprascapular nerve blocks in treating a painful shoulder and of combined supravascular and stellate ganglion blocks in treating cases of definite or even threatening shoulder-hand syndromes.

Pain in the hemiplegic side which is of *central origin* may not start until a few months after the stroke or may have increased by that time. This is another factor making early ambulation imperative because in borderline cases the patient may continue walking despite the pain; however, if for some reason the rehabilitation program is not started immediately, such a patient may resist starting to learn to walk because during the delay the pain has progressed beyond the limit of his tolerance. Mild pain of central origin usually will not interfere with ambulation and activities of daily living training. Marked pain may preclude any physical rehabilitation. "All over" pain, including the so-called good extremities, is an especially poor prognostic symptom.

When a patient's mild pain of central origin develops into severe pain, it is seldom recognized as possibly being caused by the superimposition of *pain from peripheral lesions*. Some of the success we have had with stellate ganglion blocks on the side of the hemiplegia partially relieving thalamic pain can probably be attributed to their effects on the superimposed shoulder-hand syndrome. Therefore, a pain-producing local lesion in a patient who suffers central hemiplegic pain should not be neglected because it may grow into an untreatable syndrome with a poor prognosis for the rehabilitation of the patient.

Aphasia: A great deal of clinical experience is necessary to be able to prognosticate recovery from aphasia. Schuell[7] has worked out a classification of aphasia and has attached a high prognostic value to each group; however, its use is limited to professional speech pathologists. Boone[4] is developing a speech profile index which will have good prognostic value even when used by people with limited experience in speech pathology. Receptive aphasia, and sometimes even global aphasia, does not basically interfere with the hemiplegic patient's ability to learn to walk, dress and feed himself.

Mental Derangements: We still do not have a good understanding of the derangements of higher psychologic functions that occur in hemiplegic patients, nor do we understand how they influence the prognosis for rehabilitation. Some of the confusion demonstrated by a hemiplegic patient who has been recently admitted to a hospital may be transient. The patient

may be suffering the consequences of brain edema, may have difficulties in adjusting himself to the new surroundings in the hospital or may have fleeting symptoms of apraxia. Different degrees of denial of disease are reportedly very common in the acute period.[8]

Motivation: Once the clinical picture is settled, the patient's acceptance of his disability can greatly influence the success or failure of rehabilitation, or in some cases can prolong the period of treatment. For instance, a patient who insists that his functionless upper extremity will improve in spite of what he has been told, may not be able or willing to learn one-handed self-care technics.

We have a poor understanding of what is called lack of motivation, and this term has been too often misused, especially in the field of rehabilitation of the aged. Nadler and Shontz's factor analysis of motivation,[9] using a hospital population in which the largest single group involved hemiplegic patients, bears promise of better methods of predicting the outcome of rehabilitation of the handicapped.

Body Image: The brain-injured person's image of his own body, his concept of his body in space and his perception of the outer world are still other factors about which we must learn more and find methods to evaluate their role in rehabilitation training. Bruell[2] found a high statistical correlation between a hemiplegic patient's degree of visual disturbance in space perception and his ability to learn to walk safely. Fink[10] described a way to measure some aspects of what is called body image, and thus opened an avenue for further studies leading to a better understanding of some facets of the process of rehabilitation and its success or failure. Bruell and Simon[3] recently concentrated on the development of objective predictors of recovery in hemiplegic patients.

Comments

The growing number and better quality of long range, postrehabilitation follow-up studies will doubtlessly give us a better understanding of the natural history of some chronic diseases and disabilities, and thus enable us to establish more reliable tests to predict the prognosis for rehabilitation of the older adult and the aged hemiplegic patient. It is worth while to mention here two such studies; an evaluation by Lee et al.[11] of rehabilitation of patients with hemiparesis or hemiplegia due to cerebral vascular disease, and a very promising follow-up study by Stroud[12] which covers many aspects not included in previously published literature on this subject.

We are well on the way to having well documented and properly analyzed prognostic findings which will enable the medical and ancillary professions to provide the hemiplegic patient with the best available services without the waste of skill, time and funds in pursuing aims which are beyond the patient's capabilities.

Summary

The frequency of cerebral vascular accidents and the time expended by medical and ancillary personnel on the physical treatment of hemiplegic patients make it imperative that methods be sought for a greater ability to predict the results of physical rehabilitation. The influence of different factors, particularly the type of motor involvement, the degree of sensory deficit, visual disturbances, bowel and bladder control, contractures, local and thalamic types of pain, speech disorders and abnormalities of higher psychologic functions on prognosticating physical rehabilitation of adult hemiplegic patient has been discussed.

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Potential Reversibility of the Hemiplegic Posture

Results of Reconstructive Surgical Procedures*

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DESPITE AN increasing interest among physicians in the reduction of the motor handicaps resulting from cerebrovascular disease, relatively few patients progress in motor skills beyond those of the classic hemiplegic posture. Regardless of the treatment employed, recovery of motor function is usually sufficient in the lower extremity to permit ambulation although the gait may be cosmetically undesirable and functionally unsafe. In the upper extremity there is such selective motor recovery in the flexor muscles that the normal kinetic balance between flexors and extensors is but rarely restored. This selective spontaneous return in the postural (antigravity) muscles seems little changed from the pattern portrayed in the accompanying fifty year old print (Fig. 1). From a critical viewpoint, it appears to us that the only real changes have been in nomenclature. For the expression formerly used "classic hemiplegic posture" there has been a widespread substitution of the euphemistic description of "a satisfactory rehabilitation result."

In an understandable haste to apply newer methods of treatment, too many of us have chosen to disregard this almost constant pattern of spontaneous motor recovery. Amelioration of the physical handicaps secondary to disease has been emphasized at a time when our understanding of the cause and course of the underlying disease has been less than adequate. As a consequence, much enthusiasm and effort have been spent on ever more elaborate and expensive methods of influencing motor recovery by therapeutic exercise, often without sufficient concern about either etiology or the natural history of the untreated disease.

Except for the addition of more effective means of summating afferent input (most of them derivatives of Kabat's[1] original concept of maximal resistance as the optimal proprioceptive stimulus) there have been few published departures from the therapeutic triad advocated by Kouindjy[2] as early as 1900. Kouindjy's presentation of the usefulness of re-education exercises, progressive ambulation and retraining of manual skills was greeted with incredulity by the neurologists at the International Congress of Medicine in Paris who "thought it strange that a paralytic could be made to walk." His methods were popularized in the United States by Deaver and Brown[3] and have been refined by Rusk and Covalt[4] in the past decade. Common to all of these therapeutic systems is the acceptance of *adequate* sensory input in re-education, and of early substitution of depleted functional skills by orthetic devices.

As a result of a limited control study on a group of war veterans with brain injuries, Treanor et al.[5] concluded that the Kouindjy method failed to reduce the existing imbalance between postural muscles and their antagonists. These authors advocated the careful assay and control of afferent sensory signals and particularly recommended the value of temporary "grounding" of patients and the denial of heavy tension braces. When conservative measures of treatment failed to correct the muscle imbalance, surgical means of "proprioceptive de-afferentation" were chosen. The surgical approach was offered more as an alternative physiologic postulate than as part of a therapeutic system. Its clinical by-product, greatly improved kinetic balance between antagonistic muscle groups, was therefore viewed merely as

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support for the hypothesis that motor recovery could be influenced by a better balanced proprioceptive input to spinal synapses.

In summary, it appears that all present methods used in retraining of motor function are based on the physiologic principle of *adequate* sensory stimulation. In this report, the concept of controlling afferent signals in a more selective manner by "surgical de-afferentation" of postural muscles is advanced in support of a suggested change to sensory stimuli which are both *adequate* and *appropriate*.

Material

The 184 patients upon whom surgical procedures were performed ranged in age from twenty to seventy-eight years. No attempt was made to select patients on the basis of their age and sex or the etiologic factor productive of hemiparesis (Fig. 2). The etiologic factor for the hemiparesis was diagnosed as cerebrovascular occlusive disease in 121 cases, cerebral trauma in twenty-nine cases and uncorrected infantile cerebral palsy in fourteen. Eight of the patients who underwent operation had predominantly unilateral involvement secondary to multiple sclerosis of the so-called "stroke-like" type. Twelve patients had incompletely resolved hemiparesis following brain surgery.

It must be emphasized that all the patients who underwent operation had already had an adequate program of medical rehabilitation before the benefits of surgery were advanced. It is also necessary to point out that only 184 patients were operated on out of a total of over 800 hemiparetic patients. The accumulation of this series of cases has been made possible by the generous cooperation of the sixteen surgeons who performed these procedures. The experience reported, therefore, represents the sharing of clinical results from seven private hospitals in or around San Francisco, California. All but thirty-seven of these patients were on the private services of these hospitals.

Fig. 1. Classic "hemiplegic posture" or "satisfactory rehabilitation result."

Procedures and Functional Results

Upper Extremity

Reduction of the flexed-pronated attitude of the forearm was noted in twelve patients follow-

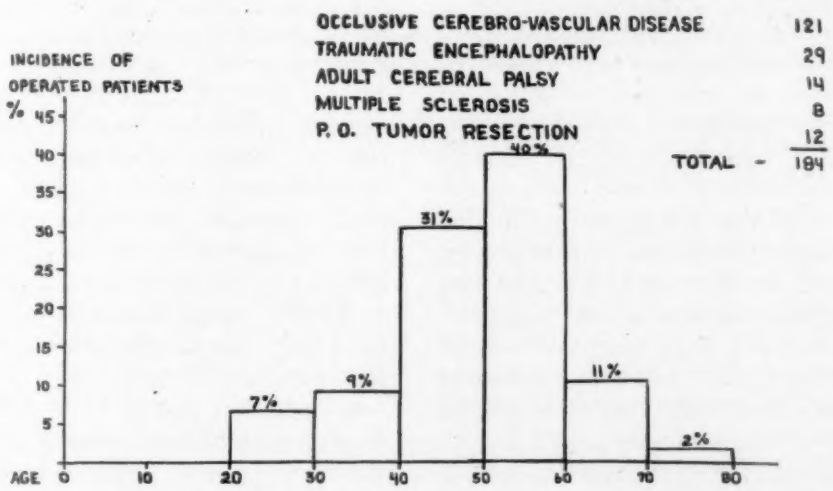

Fig. 2. Age distribution and etiologic factors in 184 patients with spastic hemiparesis who underwent operation.

FIG. 3. A, position nine years after hemiplegia. B, position after release of flexor pollicis longus, flexor digitorum sublimus and elongation of profundi to index and middle fingers. C, active extension following addition of profundus elongation of ring and little fingers. D, active flexion following same procedure.

ing tendon releases around the elbow and wrist. The tendons sectioned included the biceps brachii at its insertion into the radius, the brachioradialis and the flexor carpi radialis, both proximal to their insertions. An improved resting posture of the elbow and forearm was also associated with an increase in the speed and amplitude of active supination. The need for tenotomies at the wrist could be established by the finding of a brisk reflex pronation following percussion over the tendons.

Tendon Transfers: Early in this study, attempts to reduce the dominance of the flexor muscles at the wrist and fingers centered mainly around the use of reversible mechanical blocking, by crushing, of median axons to overactive flexor muscles. This method was soon abandoned because the results were unpredictable and because there was a relatively high incidence of postoperative causalgia. In place of it end organ procedures were substituted; initially, tendon transfers and later, tendon sectioning and lengthening. These procedures were designed primarily to increase the range and strength of the extensors of the fingers and thumb. Transfer of flexor tendons of the wrist to the common extensor tendons of the fingers and to the extensor pollicis longus was at-

tempted in twenty-one patients. Successful reinforcement of extension of the fingers was achieved in only six patients and the "in dwelling" posture of the thumb was altered significantly in only two instances.

Tendon Sectioning and Lengthening: In the past three years the employment of the technically simpler procedures of tendon sectioning and lengthening has resulted in a much higher percentage of successes. Our experience in the most recent series of twenty-four patients has pointed out the worthwhile benefits of this type of "attritional" surgery. It is clear that a better balance between antagonists can be achieved more frequently by deliberately sacrificing unnecessary hyperactivity of flexor muscles than by the previous attempts to augment extensor function by tendon transfers. In these patients the procedures which appeared to offer most toward restoration of kinetic balance were tenotomies of the flexor pollicis longus, of the flexores digitorum sublimi and lengthening of the profundus flexors.

Release of the flexor pollicis longus has been completely effective in forty-seven patients in releasing the thumb from its "indwelling position," and the procedure itself was noted to improve the excursion of finger extension in five patients. Combined with sectioning of the sublimis tendons, section of the long flexor of the thumb produced significant improvement both in the resting posture and kinetic balance in the hands of eighteen patients in whom all other methods of treatment had failed. In five patients these releases were not sufficient to correct spasticity of flexor muscles because of persisting hyperreflexia in the profundus flexors. Three of these patients were able to perform adequate opposition and finger pinching when tendons of the profundus flexors were lengthened in addition (Fig. 3A through D). In the remaining two patients the stubborn persistence of hyperactivity of the flexor muscles after all three procedures were performed necessitated reoperation. These two patients were provided with a wrist-driven flexor hinge device after performing combined tenotomies of all the sublimis and profundus flexors of the fingers and of the flexor pollicis longus.

LOWER EXTREMITY

The Rigid Knee: Characteristically, the hemiparetic patient circumducts the involved leg during the swing phase of the gait. It is apparent that part of this faulty pattern is due to the failure to initiate flexion of the knee early in the swing phase. An assessment of the relative strength of the opposing quadriceps femoris and hamstrings customarily reveals that earlier more complete recovery occurs in the extensors of the knee. In slow-motion pictures, it is evident that this motor imbalance is responsible for a temporary delay in the initiation of knee flexion. Both the speed and excursion of knee flexion are reduced by the rapid development of a stretch reflex in the quadriceps

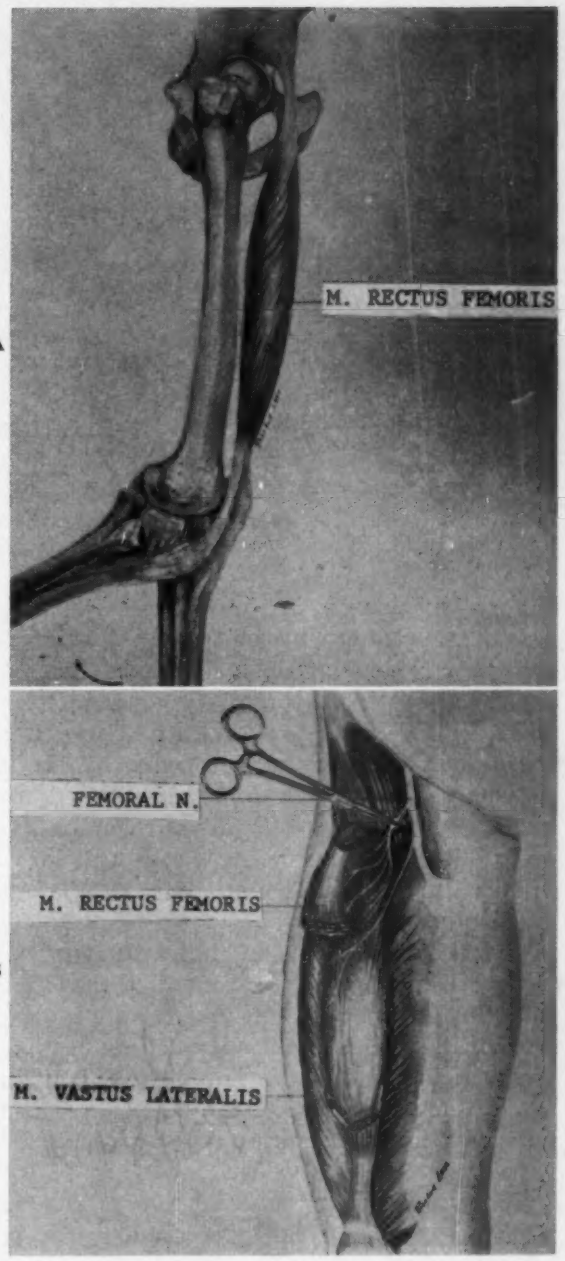

FIG. 4. A, development of rapid stretch response during early knee flexion. B, denervation of rectus femoris and part of vastus lateralis by partial femoral nerve crushing (or sectioning).

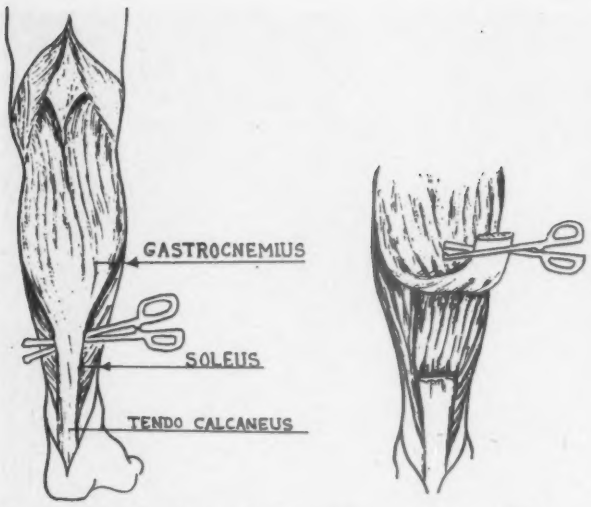

FIG. 5. Recession of the gastrocnemius. (From: STRAYER, L. M., JR. *J. Bone & Joint Surg.*, 32: 671, 1950.[6])

femoris, specifically in the more lateral fibers. Immediately after "toe-off," the rectus femoris elongates rapidly as the knee flexes, and contracts reflexly in response to this rapid stretch (Fig. 4A). The existence of this stretch response was clinically demonstrated by the improvement in knee flexion that resulted from rectus femoris tenotomy in fourteen patients, and following neurectomy or neurotripsy of branches to the rectus femoris and vastus lateralis in forty-nine patients (Fig. 4B). Reduction of the stretch response in the quadriceps muscles permitted greater ease and speed in the initiation of knee flexion and a noticeable reduction in the need for circumduction.

The Equinovarus Foot: The obvious contribution of the gastrocnemius muscle to the equinus deformity has been amply reported; this study corroborated these reports. Having had the experience of many unsatisfactory end results after thirty-nine tibial neurotripsies, we now advocate either the Strayer[6] operation for recession of the gastrocnemius (Fig. 5) or the White[7] method of elongation of the heel cord. Both of these procedures can be performed under local anesthesia and the amount of lengthening needed can be graded according to the observed improvement in the range of active dorsiflexion. Correction of the equinus attitude has been successfully accomplished in all but thirteen of ninety-two operated patients. Seven of the thirteen unsuccessful operations have been redone by sectioning the tendo achillis. Only three instances of postoperative calcaneus deformity of the foot were noted; these were so minor a degree that the patients were only

FIG. 6. Tibialis posticus hyperreflexia, a factor in hindfoot varus.

aware of the increased ease of dorsiflexion of the foot.

Correction of the equinus deformity alone offered little to the reduction of hindfoot varus. Accordingly, eighty-one tenotomies of the tibialis posticus were performed to assess the role of this tendon in production of this latter deformity. This was performed as an isolated procedure in thirty-nine patients and in conjunction with the Strayer procedure in forty-two patients. The clinical criteria for release of this tendon were the finding either of a hyperactive tendon reflex on percussion (Fig. 6) or of palpable fibrous contracture in the tendon during the passive production of dorsiflexion and eversion of the foot. It was also helpful to observe the rhythm and timing as the patient attempted to perform this motion simultaneously with both feet. In most instances the hemiparetic foot performed this synergy in two moities; namely, an initial movement of dorsiflexion in inversion followed by the completion of total eversion. Slow-motion picture studies of gait revealed a similar "check rein" of early dorsiflexion by an overactive or contractured tibialis posticus. In all but fifteen patients posticus tenotomy was performed under local anesthesia.

"Clawing of the Toes": In forty-three patients operated on for correction of an equinus or

FIG. 7. Preoperative equinus and toe "clawing." Surgical correction of equinus actually worsened the degree of "clawing."

varus attitude of the foot, "clawing of the toes" due to overactivity of the flexor muscles significantly detracted from the over-all functional result. The degree of "clawing" noted postoperatively commonly paralleled the severity of preoperative equinus and varus (Fig. 7). Also with increasing experience, it was possible to predict fairly accurately the likelihood of occurrence of postoperative "clawing," and to warn the patient that additional tenotomies might be indicated. Releases of the long flexors of the toe including the flexor hallucis longus, were eminently successful in reversing the deformity. Release of these tendons behind the malleolus also contributed to reduction of forefoot varus and, in seven patients, added to the functional improvement derived from translocation of the tibialis anticus laterally.

COMPLICATIONS AND CONTRAINDICATIONS

Complications: In view of the well known association of myocardial insufficiency with cerebrovascular occlusive states, the lack of operative mortality attests to the ease with which even patients who are poor operative risks withstand such minor surgical corrections. The morbidity statistics are outlined in Table I. *Causalgia of the hand*, occurring in five patients, was not sufficiently severe to warrant the use of energetic methods of correction such as stellate chemical blocking or ganglionectomy. *Pulmonary embolism*, occurring in three patients, and *atelectasis* in two other patients, were both considered to be due to excessive immobilization following surgery. In the patients more recently operated on, who have been mobilized promptly following surgery, there has been no incidence of chest complications. Accelerated progression of cerebrovascular disease has not been noted as a complication of this type of surgery. Patients receiving long-term administration of anticoagulants have been temporarily withdrawn from therapy for the immediate pre- and postoperative periods without apparent detriment.

TABLE I
Complications of Surgery

Complication	No. of Patients
Causalgia of the hand	5
Pulmonary embolism	3
Atelectasis	2
Overcorrection of muscular imbalance	9
Denervation fibrosis	3
Delayed wound healing	26

Naturally, the complications of *over- and undercorrection* of muscular imbalances were of primary interest to us. We had anticipated that a small percentage of overcorrection with the consequent production of a calcaneus deformity of the foot would result from the wide use of procedures for elongation of the spastic contractured heel cord. In fact, only three patients had a minor degree of calcaneovalgus of the foot following the Strayer procedure and the overcorrection did not interfere with ambulation in any instance. In two patients the transfer of the flexor carpi ulnaris around the ulnar border of the wrist resulted in excessive supination of the hand; this position was described by the patient as being both functionally and cosmetically undesirable. In four other patients, following tenotomy of the wrist palmar flexor tendons, there was a noticeable reduction in the amplitude and speed of finger extension as a consequence of the newly provided dorsiflexed position of the wrist.

In the great majority of patients, however, errors were made on the side of undercorrection, and reoperations were necessary either because of too rapid reinnervation or because of insufficient lengthening of the tendon. In three patients, crushing of the tibial branches to the gastrocnemius-soleus complex resulted in considerable *denervation fibrosis* within these

muscles; in all three patients the equinus deformity was actually accentuated by surgery.

Delayed healing was most common at the elbow, wrist and ankle. The lower one-third of the leg is recognized as having poor vascularity and in this series this contributed to delayed skin healing in twenty-three patients. However, we noted that this complication could be minimized by the use of a walking cast in patients whose vascular supply was considered to be inadequate preoperatively.

Contraindications: Four major reasons which prompted us to reject patients as candidates for surgical corrections are as follows: (1) advanced thalamic state; (2) agnosognosia; (3) profound proprioceptive loss; and (4) lack of enthusiasm in patient (this is *elective* surgery). First, patients with persistent, poorly localized pain in the extremity (the so-called *thalamic state*) were rejected because the addition of further foci of nocioceptive stimuli merely compounded the existing kinetic dysfunction. The wisdom of this choice was made apparent to us in two patients with thalamic pain, whose postoperative recovery periods were almost as trying on the surgeon as they were unpleasant for the patient. Existence of the organic deficit, described by Critchley[8] as *agnosognosia*, was in our experience another absolute contraindication to the use of surgical procedures. Expressed either as a denial of the paretic limb or as a wholly unrealistic appraisal by the patient of its functional usefulness, this state was noted only in patients with such extensive brain damage that retraining by any method was completely futile.

It was also revealed to be wiser to refrain from surgical corrections in patients with a *gross proprioceptive deficit*. In four patients the functional benefits derived from surgery were greatly reduced by the existence of inadequate appreciation of position sense, particularly about the hand. The last major contraindication to surgery needs little emphasis. These surgical means of helping in the retraining of imbalanced muscle states are obviously elective procedures and any *lack of enthusiasm on the part of the patient* should always be interpreted as another absolute contraindication to surgical methods.

Comments

It is obvious that the method advocated in this report has such wide clinical and sociologic implications that it could be advocated only after an extensive clinical trial. Because of the numerous changes in the type of surgical procedure employed, each of these procedures has been investigated postoperatively for a period of at least two years before publication. Moreover, our interest was centered not so much in the assessment of the merits of individual surgical procedures as in the influence of surgical de-afferentation on synaptic conduction. Success of the surgical approach was, therefore, to be judged not so much by the reduction of spastic contracture or hyperreflexia but by the motor increments seen in the previously depressed antagonist.

The major criticisms directed against the employment of these procedures are that they are clinically unnecessary, that they are expensive and potentially dangerous and that they have application only to young adult patients. The label *unnecessary* has been applied because others have felt corrective bracing of the extremity can accomplish the same results as surgery. In our experience, the advantages of bracing for the "correction of spasticity" have been greatly exaggerated. Indeed, at times we have been impressed with the increase in spasticity of the postural muscles that follows heavy tension bracing to correct these overactive muscle groups. Moreover, we have not seen any increments in the strength of a hypoactive muscle result from mechanical stretching of its overactive antagonist by tension braces. According to our hypothesis the only rational and physiologic means of influencing the prevailing spinal relay system must be through reduction of afferent "feed-back" from these overactive muscles.

To the criticism that these procedures are *potentially dangerous* we can point to an operative experience of no deaths and very low morbidity. With increasing experience, we come to view these procedures as mere incidents in the over-all pattern of spontaneous motor recovery, as means of encouraging recovery in a selective purposeful fashion. We have, as yet, made no detailed analysis of the *financial aspects* of this method but it appears that the earlier employment of surgical corrective measures greatly reduces the need for physical rehabilitation in many adult hemiparetic patients. Too often, the convalescence of these patients is unnecessarily prolonged because of the physician's lack of awareness that minor surgical procedures may favorably influence the pattern and speed of motor recovery.

Chronologic age of itself seemed to have little influence on the success of the surgical procedures. Indeed, these procedures had even wider usefulness in older patients because significant improvements in kinetic balance were acquired much more speedily by surgical means than by therapeutic exercise. The patient with coexisting myocardial and cerebrovascular disease is an acceptable candidate for minor surgical corrections of deformity. In such a patient the often strenuous demands of resistive exercises may lead to further embarrassment of an already inadequate cardiac reserve. We therefore advocate these procedures because they are physiologic, relatively inexpensive compared to the cost of the prolonged rehabilitation by conservative means, suitable for all age groups and extremely safe when employed in the proper patient.

Clinical Applications: It is implicit throughout this report that this method has its greatest application to the problems of the spastic lower extremity. It is postulated that the "classic hemiplegic gait" is compounded of the rigidly extended knee and of an equinovarus foot. These functional impairments lend themselves easily to surgical correction or amelioration. There is no comparable degree of assured functional improvement following any of the procedures we have investigated for improvement in the arm. Our principal interest in the upper extremity has been in reducing the afferent "reflux" from hyperactive flexor muscles of the fingers and thumb.

We have been impressed by the fact that many of these tendons are in fact "disposable," and that their removal is not reflected in any functional decrement but rather in an improved posture at rest and kinetic function. Furthermore, the improvement in posture of the hand that results from tenotomies of the flexor pollicis longus and the sublimis flexors may permit the revival of many of the previously abandoned tendon transfer procedures in the hand. For an earlier and still widespread attitude of hasty, reckless abandonment of the involved hand, we are proposing closer study of the individual components of flexor hyperreflexia, in the belief that selective de-afferentation can make possible surgical reconstruction of improved function.

With increasing experience in the use of these procedures, we have acquired a mounting curiosity about the correct timing of surgery. The concept that surgery should be considered as a means of preventing muscular imbalances rather than as a means of correcting them has been explored successfully in a few patients. It has also been our experience that a much higher percentage of patients with developing spasticity in the flexors of the fingers can be improved if earlier surgical corrections are carried out.

Obviously, these procedures will have greater attractiveness to the referring physicians if most of them can be done on a "come and go" basis, and also under local anesthesia. It was primarily for these reasons that we chose to investigate the possible benefits of "soft tissue surgery," and have not included our experience with joint arthrodesis in this report. In this series, it has been demonstrated that tendon releases including the release of the gastrocnemius can be successfully performed under local anesthesia. It is hoped that improved technics in the future will permit all the operations including tendon transfers to be performed under local anesthesia and during very short periods of hospitalization. Under these circumstances it is believed that the method will have increased interest for referring physicians and that further technical improvements will follow its more widespread acceptance. Surgery must be considered as a supplement to rather than as a substitute for existing methods of functional retraining. Its use should, therefore, be reserved for those patients in whom nonsurgical means have failed or are failing to alter the pattern of spontaneous motor recovery.

Summary

The use of well known reconstructive surgical procedures for the correction of muscular imbalances in the patient with adult spastic hemiparesis has been outlined. These procedures have been used on 184 patients, varying in age from twenty to seventy-eight years, with a wide variety of etiologic factors productive of hemiplegia. The principal aims of surgery in the upper extremity were the reduction of the flexion-pronation attitude of the elbow and the correction of the flexor predominance at the wrist and fingers. In the lower extremity, our goals were the improvement of the speed and range of knee flexion, an increased range of dorsiflexion of the ankle and reduction of the varus deformity of the foot.

In the upper extremity functionally successful results were obtained in thirty-five out of seventy-five patients who underwent operation,

an incidence of 46 per cent. In the lower extremity successful results were obtained in 129 out of 154 patients operated on (84 per cent). The most rewarding procedures were the Strayer method of recession of the gastrocnemius, the White method of lengthening of the heel cord, release of the tibialis posticus tendon, translocation of the tibialis anticus tendon laterally and nerve interruptions of femoral branches to the lateral heads of the quadriceps.

No death due to surgery was reported in the series; the morbidity encountered was surprisingly low. Four major contraindications to surgery are discussed and a physiologic rationale for this method of treatment is advanced. A plea is entered for a more rational approach physiologically to the underlying muscular imbalances and their correction. Substantiation of our hypothesis that the hemiplegic posture is indeed potentially reversible in a considerable proportion of patients must obviously await the employment of these principles in larger groups of patients.

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Psychiatric Considerations of Cerebral Vascular Disease*

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A DISCUSSION OF THE psychiatric aspects of cerebral vascular disease would seem to fall logically into three categories as follows: first, the role of psychologic factors in the causation or precipitation of the disease; second, the psychiatric consequences of cerebral vascular disease; and third, the management of these consequences. Because this symposium is concerned primarily with the rehabilitation of patients with cardiovascular disease this article will be limited to the second and third categories.

PSYCHIATRIC CONSEQUENCES OF CEREBRAL VASCULAR DISEASE

The psychopathology which occurs following lesions of the brain secondary to cerebral vascular disease is now regarded not only as an expression of changes in the structure and function of the brain but also as an expression of the efforts of the brain-damaged personality to adapt to the perceived defects in function and to those demands that can no longer be met because of these defects. The effort of such patients to find a new adjustment results in the following three types of symptoms. The first expresses the conflict which the subject faces; the second reflects the tendency to build substitutive performances in order to adapt to the demands of the environment in the most effective manner under the circumstances of defect; and the third is the direct result of the impairment of the functioning of the brain itself.

We believe it convenient to think of the human organism as consisting of a body and a personality in contact with the external world, animate and inanimate. To fully understand a person, his functioning must be evaluated in each of these areas as well as the relationship between them. When a person suffers cerebral vascular disease, each of these areas of functioning is affected. It can impair the use of his body as a tool with which to experience and manipulate the environment. Sensation and perception of the external world may be disturbed as a result of blindness, damage to sensory input and brain damage so that awareness of the external world and internal perceptions are disordered. The motor system is often affected so that locomotion and essential movements are impaired. The disability may disrupt personality dynamics and equilibrium and threaten a way of life. It may cause intense anxiety, depression and rage. It may be interpreted as punishment for sins real or imagined and lead to profound guilt. It may threaten normal mastery of the environment and produce feelings of helplessness and panic. It may unloose previously controlled psychopathology such as paranoid thinking and create intolerable interpersonal relationships. It may be organized into the patient's neurotic strivings such as dependency or fear of competition and be unconsciously welcome as a way out of a conflictive struggle. Finally, the disability removes the person from normal social experiences and from work situations which are major sources of satisfaction and self esteem. Disruption in family life and friendships, separation from loves ones, economic problems, shattered ambitions and dreams—all are threats to the patient.

Cerebral vascular disease, then, represents a massive assault on the organism. How he reacts will depend on the nature of the disability, the reality problems it creates, the personality of the subject, his past history and life experiences, the meaning of the disability both

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conscious and unconscious and the resources provided by the patient, his family and society.

INTELLECTUAL FUNCTION

Kanner has defined intelligence as "the capacity to think, solve problems and analyze situations in life." He emphasizes that intelligence is not a separate area or compartment of mental functioning but merely one aspect of an integrated function of the organism. However, it is apparent that to function intelligently the organism must have the capacity to learn, which in turn depends on memory and on associative ability, his judgment must be adequate, he must have the capacity for abstract thinking, etc. Not all patients with cerebral vascular diseases exhibit evidence of damage in these areas.

The clinical dictum that memory for recent events is first to go can be validated by clinical experience. This is one reason why elderly people tend to dwell in the past. If this past experience has been a rich one the patient may be able to function surprisingly well, drawing on this rich storehouse and using it in a clever manner.

It is not always easy to diagnose impairment of intellectual function on direct examination; some patients may require more subtle psychophysiologic tests.[1,2] In overt cases the diagnosis is fairly clear-cut. The patient is forgetful, may be disoriented for time, place and person, may wander and get lost and is unable to manage his daily affairs, monetary or otherwise. Such patients frequently demonstrate fluctuations, being clear one day and quite confused the next.

On occasion amnesia will occur and one is confronted with the problem of differential diagnosis of organic and psychogenic amnesia. The diagnosis of psychogenic amnesia should not be accepted unless there has been no loss of consciousness, no impairment of intellectual functions and unless a psychologic basis for its occurrence is determined. Sudden and complete recovery of memory is not uncommon in cases of psychogenic amnesia but does not occur if the amnesia is caused by organic factors. Any recovery of memory that has been lost through organic factors takes place gradually and is often incomplete.

DEPRESSION

It is inevitable that so long as consciousness or awareness is present the patient with cerebral vascular disease will experience a variety of emotional reactions such as anxiety, depression and rage. Of these the most common and persistent is that of depression. This may vary from a state of mild sadness to the extremes of psychosis and suicide. The degree of depression is determined not only by the nature of the disability but also by the particular patient who suffers it and the special meaning it has for him.

In the milder forms of depression the patient is quiet, inhibited, unhappy, self depreciative, discouraged and disinterested in his surroundings. In more severe depression there is a constant unpleasant tension. Every experience is mentally painful. The patient's interests are very limited and always melancholy. Conversation is difficult and he is dejected and hopeless in attitude and behavior. Insomnia, especially that due to early awakening, is common. Somatic complaints such as constipation, loss of appetite, fatigue, tightness of the head and headaches, are frequent. Delusions may appear and usually express ideas of guilt, unworthiness and self accusation. Suicidal thoughts are often entertained. When elements of anger and anxiety are present the patient may become agitated. It should be pointed out that patients often defend themselves against depression either by means of somatic preoccupation, or by means of compensation such as cheerfulness, euphoria and even hypomanic and manic behavior.

Depression is always associated with a sense of loss and is allied with feelings of grief. It is not uncommon for the physically disabled patient to personalize his body or parts of his body and feel toward it as he does toward a cherished person. Loss of function of any part of the body is reacted to in much the same fashion as one reacts to loss of a loved person.

Guilt feelings lead to depression. The guilt may be for real or imagined sins, and all kinds of experiences are dredged up from the past to explain the accident and to heap blame on oneself.

Loss of Self Esteem: Central to the depression observed in cerebral vascular disease is loss of self esteem, so much of which is derived from a sense of mastery. This mastery has developed from our earliest years in the process of maturation; we have learned to walk, talk, control our bladder and bowels, dress ourselves, wash and perform literally hundreds of other activities. These skills are acquired in a social matrix in-

volving parents and teachers, and out of these skills comes a sense of mastery which leads to confidence and self esteem, or if our experiences have been associated with destructive relations with parents or teachers to a lack of confidence and self esteem. When a physical disability strikes, many of these skills and controls are lost, some permanently. The patient is projected back into a childlike, helpless state and this regression leads to depression, particularly if the acquisition of these skills was associated with earlier traumatic experiences.

The patient with brain damage suffers acutely from such depression even if there is no peripheral paralysis or sensory loss. The awareness of damage, however slight, to the most valued organ in the body, the brain, so essential to everything considered human, is particularly painful and the sense of inadequacy, of doubt as to ability to cope with life and its demands, always leads to depression.

ANXIETY

Just as depression is inevitable following cerebral vascular diseases, so is anxiety. By anxiety is meant a condition of heightened and often disruptive tension accompanied by the vague and disquieting feeling of prospective harm or distress. Basically, anxiety is a biologic signal of anticipated danger.

Patients with cerebral vascular diseases are fearful of dying. The acute onset of the illness, often associated with loss of consciousness, is very frightening and the patient lives in constant fear of another episode. In the slowly progressive types such as senility and arteriosclerosis, there is a feeling of disintegration, that forces are at work over which the patient has no control. The awareness of physical defect, inability to move an arm or leg, inability to remember, produces a feeling of helplessness with anxiety and sometimes panic. Perceptual insecurity with difficulties in apprehending and integrating experience is a common cause of anxiety.

When the anxiety is intolerable or unacceptable to the patient a variety of defenses are brought into play; often it is these defenses which present themselves as psychiatric symptoms and which often determine diagnosis. Anxiety may be repressed from conscious awareness. It may be displaced to an object or situation to produce a phobia. It may be converted into an hysterical symptom. It may be controlled or walled off by means of obsessions and compulsions. Behavioral mechanisms such as apathy, boredom, hyperactivity or compulsive flow of speech may be utilized to express or contain the anxiety. It may lead to psychosomatic disorders or to hypochondriasis.

"*Catastrophic Reaction*": Aside from the usual symptoms of anxiety and its defenses, the patient with brain damage manifests what is now commonly known as the "catastrophic reaction."[2–4] Confronted with a problem he cannot solve the patient becomes suddenly anxious, agitated and may appear dazed. His color changes, he fumbles, and autonomic disturbances such as irregular pulse and respiratory rate appear. He may become evasive, sullen, irritable and even aggressive. The "catastrophic reaction" develops simultaneously with the attempt to perform the task in which he fails and not following the performance; it does not appear to depend on the patient's awareness that he has failed. As a result certain behavioral patterns evolve in many patients with brain injury. Some, when confronted with tasks they cannot solve, lose consciousness. Others avoid exposing themselves to such situations by isolating themselves or by avoiding tasks through apparent inability to understand directions. Some are impelled into continuous activity, leading in some cases to "occupational delirium." Others adapt through an excessive orderliness, any deviation from which produces anxiety.

DENIAL

Although the patient with cerebral vascular disease demonstrates the ability to utilize all the defenses against anxiety and depression which are available to those patients without brain damage, there is one type of defense which he demonstrates more commonly, and that is denial. In 1914 Babinski applied the term *anosognosia* to those patients with left hemiplegia who completely denied or were unaware of their paralysis.

For many years observers believed that this phenomenon occurred only in patients with brain damage and even went so far as to localize the lesion in the right side of the parietal cortex. However, recent workers have disputed this localization and have described denial in patients with all types of disordered brain function. In addition, denial has been described in disabled patients without brain damage, such as with paraplegia and amputation.[5]

Nathanson et al.[6] found verbal anosognosia for the paralysis in twenty-eight of 100 hemiplegic patients admitted consecutively to a general hospital.

Weinstein and Kahn,[7] in a study of 104 brain damaged cases, classified denial according to explicit expression in verbal terms, and implicit expression in terms of feeling and behavior. An example of the former is the patient who, when asked to move the paralyzed arm, moves the unparalyzed one or denies paralysis of his arm but states the arm of the nurse is paralyzed. An example of the latter is the patient who admits to paralysis, but whose goals for rehabilitation may be totally unrealistic. The mood of patients with explicit verbal denial is usually bland and affable during interviews and they have been described as showing "fatuous equanimity." Anxiety in the ordinary clinical sense is absent. Euphoric, hypomanic, paranoid and depressed attitudes are more prominent in the group revealing implicit denial.

Why denial occurs more frequently in the patient with brain damage has been the subject of much speculation. It has been suggested that denial of disability occurs on the basis of structural damage to the brain; that there is a failure in perception and that incoming stimuli are either not perceived or are perceived incorrectly. It has also been suggested that motivational factors are dominant, that the denial can be explained on the basis of personality needs and wish fulfillment. Probably both factors operate to a varying degree in different patients.[8]

PERSONALITY CHANGES

Cerebral vascular diseases may be ushered in by a variety of symptoms depending on the nature of the disease, location, extent, whether acute as in embolism or insidious as in senility. There may be a sudden loss of consciousness, a variety of neurologic symptoms; the very first evidence of the disease may be a change in the personality of the patient. This change may appear suddenly or it may be subtle and progressive. It may be the first and only sign or it may follow or be associated with more strictly physical signs of illness.

The main causes of the slowly progressive types are cerebral arteriosclerosis and senility. The differential diagnosis between these two conditions is not always easy; a clear-cut correlation between pathologic findings and the presence or absence of psychiatric symptoms does not exist. In classic psychiatric nosology, however, the two conditions are differentiated.[9]

Arteriosclerosis: The age of onset of the arteriosclerotic psychoses is generally between fifty and sixty-five years. Prodromal symptoms in the form of fatigue, headache, dizziness, diminution of capacity for prolonged concentration, drowsiness in the afternoon or evening and an insidious impairment of physical and mental abilities are common. Not rarely, latent character traits are revealed or previous trends become pathologically exaggerated. Episodes of confusion or excitement or their combined association constitute a frequent symptom of the arteriosclerotic syndrome. In other cases the onset is insidious and represents what has been described as "a slow dying at the top." Among such symptoms are easy mental fatigability, a lessening of initiative, impairment of attention, emotional instability with outbursts of weeping or laughter and a tendency to depression. Some patients become garrulous; others are irritable, aggressive, meddlesome, quarrelsome, obstinate, jealous and paranoid. Neglect of personal appearance is not uncommon. Defective judgment and decreased inhibition may result in sexual indiscretions or offenses. Memory is impaired to varying degrees; at first it may consist merely of difficulty in recollecting names but later becomes general. Daily fluctuations are common.

Senility: This condition occurs usually at a later age and is more common in women than men. The transition from usual old age to senile dementia is ordinarily gradual and a decision as to when the line has been crossed is often arbitrary. A dislike of change, a tendency to become constricted and self centered in interests, an increased difficulty in comprehension, a tendency to reminisce and to repetition are early signs. Memory difficulties, starting with loss of memory for recent events, appear early. A tendency to isolation occurs. Deterioration may continue to almost complete regression.

Personality Changes Following Acute Episodes: In the acute episodes following thrombosis, hemorrhage or embolism and assuming absence of or recovery from coma, one is more likely to see affective disorders such as anxiety, depression and denial, as described previously. Usually the presence of paresis, paralysis, aphasia or hemianopsia, the more frankly neurologic symptoms, gives rise to a more acute psychiatric

picture. Following recovery and entry into the chronic stage the personality picture will depend on the extent of the brain damage and the previous personality of the patient.

One of the most distressing developments is that of dependency or invalidism because it places a great burden on both staff and family and tends to generate considerable hostility. The patient is unable or unwilling to do things for himself, is demanding of attention and service and generally complains of the inefficiency of the hospital, staff and family.

Management of Psychiatric Problems

The delineation of psychiatric problems resulting from cerebral vascular diseases is obviously not an exhaustive one. Their selection has been based both on their frequency of occurrence and on their influence on rehabilitation procedures. It is assumed that following an acute cerebral vascular episode as well as the appearance of the progressive arteriosclerotic and senile diseases not only will active therapeutic measures be instituted but modern rehabilitation technics will be employed.[10]

Evaluation of Prognostic Factors: The outcome of rehabilitation in cerebral vascular diseases depends on a multiplicity of factors. Recent studies[11] have emphasized the importance of the extent of brain damage as well as psychosocial factors. Of particular importance is motivation; this obviously depends on a vector involving the total patient including body, personality and environment. While physical factors such as degree of neurologic defect were of importance in the individual patient, they seemed to exert little influence on the results obtained in the group as a whole. The importance of social and psychologic factors seems to have been outstanding.

Rehabilitation is mainly a training and learning experience; therefore, a basic minimum of cerebral function is necessary. Those patients with extensive organic brain damage usually do poorly in rehabilitation. Because of the severe memory defect they cannot remember from day to day what they have learned. Because of perceptual difficulties they have difficulty in knowing their position in space, in learning to walk or in learning occupational technics. However, caution must be exercised in evaluating such patients. If they are seen soon after the acute episode the picture may look very grim. Weeks or months later the outlook may be much more optimistic. With moderate or mild brain damage much can be accomplished in rehabilitation. As has been mentioned, many patients with cerebral vascular diseases reveal no overt evidence of disturbance of mental function. If this is so, then they can be treated as any patient with no brain damage. The program should be geared to help the patient work with the deficits that he has. Untoward emotional reactions are probably due to reactions to the disability or to factors other than to the brain damage itself. Such patients can be helped by insight as well as supportive psychotherapy.

Organic Changes: Those patients who exhibit signs of organicity require special treatment. Rehabilitation program and goals are generally more limited. The milieu must be a peaceful one without distractions. Special effort is made to keep the patient's environment constant so that therapists and classes are stable. Fewer activities are prescribed simply because the patient with brain damage has difficulty learning when exposed to too many tasks or demands at one time. A great effort is made at repetition and drill in teaching. Many trials are necessary to attain mastery in a skill and these trials are spaced rather than massed together. The patient is informed of his progress and is always made aware of his immediate goals. Despite the gentleness necessary in managing the patient with organic disease, firmness and decisiveness are important. A firm therapist presents a fixed, predictable stimulus figure in a world which has become otherwise disordered in the patient's view.

Sudden changes in environment are often the cause of serious emotional distress in patients with organic disease. Moves from home to hospital, from hospital to a rehabilitation center and from center back home all tend to precipitate severe anxiety and depression and, on occasion, acute psychotic episodes. Many of the emergencies calling for psychiatric consultation occur on admission or just before discharge.

Depression: When depression is present, in most cases it is of a reactive type, appropriate and related to the cerebral insult and as such responds well to relatively superficial psychotherapy such as support and understanding. Engagement in the rehabilitation program is very helpful, draining energy and anxiety and preventing ruminative preoccupation with self and with body. When the depression is more

severe and psychomotor retardation and inhibition are evident more intensive therapy is indicated. Antidepressant drugs such as Ritalin,® monoamine oxidase inhibitors or imipramine are indicated. It is too early to say whether the drugs will completely replace the physical therapies such as electroshock.

Insomnia: Patients with cerebral vascular disease often complain of insomnia and one is tempted to use barbiturates in such cases. This is unwise because they tend to become agitated and confused. Use of a tranquilizer such as meprobamate, or in more tense and agitated patients one of the phenothiazine group, is particularly effective. In the case of an agitated depression a monoamine oxidase inhibitor can be used in the morning and a phenothiazine tranquilizer at night. (It should be emphasized that special attention be given to dosage, contraindications and side effects. The newer psychopharmacologic agents seem to be more potent in the elderly and in the patients with brain damage.)

Anxiety: Management of anxiety depends on an evaluation of its sources as well as on the diagnostic nature of the symptom. Depending on the qualitative and quantitative aspects of anxiety and its defenses and modes of expression, the individual subject's behavior is called reactive, neurotic or psychotic. In the reactive types the anxiety is related to reality factors and may be estimated by the observer to be appropriate to the situation. In the neurotic patient the anxiety is considered to be quantitatively greater than the situation calls for or is being expressed in neurotic mechanisms such as phobias, hysteria, etc. The roots of neurotic anxiety will be in earlier unresolved life situations, so that the subject organizes the present real situation into a previous one and reacts to it on the basis of these earlier perceptions. In the psychotic patient the anxiety is so overwhelming that it disorganizes mental functioning, leading to a gross break with reality.

The reactive and mildly neurotic forms of anxiety respond to support, a sympathetic milieu and rehabilitation procedures. Physical activity provides an outlet for release of tensions. Rehabilitation in a group setting also has the advantage of lending support of other patients and helping to remove the feeling of estrangement and uniqueness so often associated with disability.

The more severely neurotic anxiety requires more intensive psychotherapy plus the use of the tranquilizers. Psychoses are treated in the appropriate fashion by the psychiatrist.

Denial of Disability: This condition poses a contradictory problem. On the one hand, it may seriously interfere with rehabilitation which demands a recognition of the disability and an understanding of the various procedures; on the other hand, it is an important defense of the ego, a crutch so to speak, without which the patient may be overwhelmed by depression and anxiety. Resolution of this paradox depends on a careful evaluation of the patient's status and resources. In cases of complete denial attempts at suggestion or logical argument are futile. Gross attempts to break through the denial may precipitate an acute psychiatric emergency. Rather than attempting to deal with the denial directly the patient should be treated for his physical disability. Every effort should be made to engage the patient in rehabilitation procedures which are introduced gently and slowly. Time and milieu will become effective slowly if at all. When denial is implicit and there is considerable emotional lability tranquilizers and psychotherapy are used.

Personality Problems: The management of personality problems is most difficult and is the cause of considerable guilt and conflict in the family. Too often the patient is whisked off to a mental hospital[12] or to a nursing home where he deteriorates rapidly. On the other hand, the lapses of memory, the disturbed judgment, the loss of habits and cleanliness, the paranoid or domineering behavior may be literally more than a family can manage so that some disposition is essential.

We know that the changes observed are due not only to physical and biologic factors but also to psychosocial ones. The loss of status, the loneliness, inactivity and boredom give rise to many of the disturbances which are observed in the elderly. Active social rehabilitation measures can effect marked changes in behavior and even serve as a prophylactic against senility. The experience of "Golden Age" clubs bears this out.[13]

Every effort should be made to care for the patient at home. Even in the presence of gross disturbances such as the delusions, management can be effected at home.

Whether treated at home or in a nursing home or in a hospital a carefully regulated mode of life is required. An agreeable occupation should be continued as long as possible provided

it does not carry with it burdensome physical labor or mental tasks. Social and recreational opportunities are necessary.

Of equal importance is the understanding and cooperation of the family, which may require group education and psychotherapy. The patient with cerebral vascular disease is particularly dependent on acceptance by the family, and the family, too, needs understanding and help in dealing with what usually is a trying emotional and physical problem. As in disabled children, motivation of the elderly, disabled patient is derived in large part from the family. Rejection is intolerable.

Aphasia: Finally, a word about aphasia, a particularly devastating result of cerebral vascular disease. Lee et al.,[11] in 230 patients, noted this disorder in ninety-five or 41.4 per cent. They noted improvement in only 35.3 per cent of their total group. Marks, Taylor and Rusk[14] reported about 50 per cent improvement, statistic analysis indicating improvement beyond that anticipated by spontaneous restitution. The psychologic reactions of aphasic patients are generally more intense, especially in those patients who have depended on mental activity and verbal communication for their livelihood. The sense of frustration is enormous and tension may reach explosive proportions. Inability to communicate verbally or to understand, and when apraxia exists to write, make the usual modes of psychotherapy impossible. And since the results of training in aphasia often lead to failure, and when improvement occurs it requires long and patient effort, the difficulties are compounded. Depressions and agitations can be managed with psychopharmacologic agents but our limited experience indicates that they do not facilitate relearning of speech. Group speech therapy has been noted to be of some help. These patients require more attention than those without aphasia.

Summary

1. Psychiatric factors in the precipitation of cerebral vascular diseases are reviewed. A physiologic basis for the effect of emotional stress on cerebral circulation does exist. However, beyond the clinical observation of the temporal association between such stress and the onset of acute cerebral vascular disease in individual cases, no other type of acceptable evidence is available at the present time.

2. Psychiatric consequences of cerebral vascular diseases are described. Theoretical considerations are discussed; clinical problems associated with disturbances of intellectual functions, depression, anxiety, denial of illness and personality changes are presented.

3. Management of these clinical problems is suggested. These include milieu therapy as well as the traditional modes of psychotherapy and pharmacotherapy.

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Clinical Studies

The Effect of Guanethidine in the Treatment of Hypertension

A Study of Twenty-Five Patients*

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THE GANGLIONIC BLOCKING agents have been a valuable adjunct in the treatment of hypertension which does not respond satisfactorily to the administration of less potent antihypertensive drugs. The untoward effects associated with parasympathetic blockade, however, have limited their usefulness in many patients with severe hypertension.

Guanethidine (SU-5864)†, one of a group of compounds synthesized by Mull and coworkers,[1] was demonstrated to have a blood pressure lowering effect in hypertensive dogs with renal and neurogenic disease.[2–4] These hypotensive effects are marked and prolonged following a single intravenous dose; similar results have been obtained after oral administration. More recently it has been demonstrated[5] that guanethidine depletes the norepinephrine level in the hearts of rabbits and cats. It is believed that a similar effect takes place in the arteriolar wall; a depletion of norepinephrine at this site results in marked reduction in blood pressure without parasympathetic blockade. Recent investigations in human patients using guanethidine have indicated that it is an antihypertensive agent of considerable promise.[4,6,7]

The purpose of this study is to report our experience with twenty-five outpatients treated with guanethidine as the sole antihypertensive agent for periods ranging from six to twenty weeks. All of these patients had chronic hypertension and were referred for study after having been previously followed from several weeks to several years in the outpatient clinics of the Philadelphia General Hospital.

MATERIAL AND METHODS

Twenty-five patients with persistent diastolic hypertension were selected for study; fifteen were women and ten were men. Their ages ranged from thirty-one to seventy-three years; the average age was fifty-five years. The average known duration of the hypertension prior to treatment was five and a half years. Of these, twenty patients had essential hypertension, one had hypertension secondary to toxemia of pregnancy and four had hypertension associated with chronic pyelonephritis. Recumbent blood pressures taken after other hypotensive medication had been discontinued for a period of at least two weeks were accepted as a baseline. These pressures ranged from 160 to 294 mm. Hg systolic and 100 to 160 mm. Hg diastolic; the mean systolic was 204 and the mean diastolic, 120 mm. Hg. Twelve patients had a diastolic pressure of 120 mm. Hg or greater, and thirteen had diastolic pressures between 100 and 120 mm. Hg prior to treatment. All patients had preliminary clinical examinations and laboratory studies which included roentgenogram of the chest, electrocardiogram, urinalysis, blood urea nitrogen, phenolsulfonphthalein and Fishberg concentration test as well as complete blood counts and liver function studies. When indicated, intravenous and retrograde pyelography were performed. These tests were repeated at the completion of this study.

Depending on the basal blood pressure reading, an initial dose of 10 to 25 mg. of guanethidine was administered daily by mouth. The blood pressure was recorded weekly and the drug was increased by 10 to 25 mg. doses until a satisfactory fall in pressure was obtained or untoward effects ensued. Because of the initial small doses used and the variable responses to treatment, at least six weeks were required for an

† This drug was supplied by Ciba Pharmaceutical Products, Inc., Summit, New Jersey.

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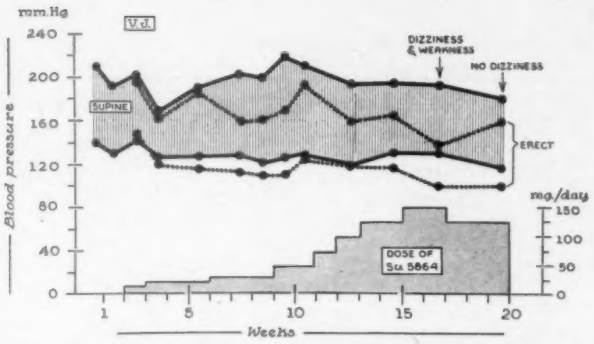

FIG. 1. Salutary effect of guanethidine in reducing the blood pressure in a fifty-seven year old woman (Case 4) with moderately severe hypertension. In this and the following figures the dotted line connects points representing the blood pressures in the erect position; the solid line, points representing supine pressures. Blood pressure has been plotted along the ordinate and weeks of study along the abscissa.

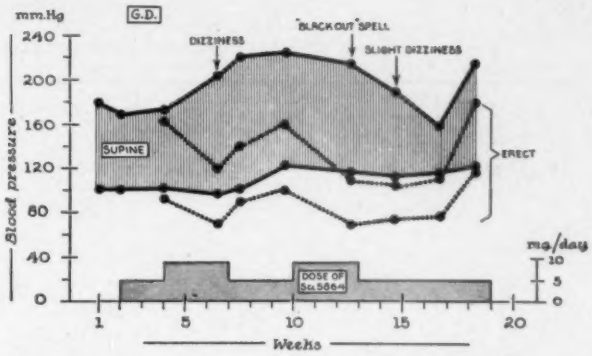

FIG. 2. Illustrates the effect of guanethidine in a patient (Case 2) with mild hypertension, generalized arteriosclerosis and chronic congestive heart failure.

adequate dosage level and a satisfactory blood pressure response to be attained in many patients. Therefore, only those patients followed for a minimum period of six weeks were included in this report.

RESULTS

There was a fall in blood pressure in response to guanethidine in all twenty-five patients. This effect was more marked in the erect than the recumbent position (Table 1). This is similar to findings previously reported.[4,6,7] The pressures fell an average of 22 mm. Hg systolic and 14 mm. Hg diastolic in the recumbent and 49 mm. Hg systolic and 24 mm. Hg diastolic in the erect position. There was no clear correlation between the initial blood pressure reading and the daily maintenance dose of the drug required to control the blood pressure. This maintenance dose varied from 5 to 200 mg. daily (average 80 mg.) and was administered either as a single dose or divided into two daily doses. Ten patients required from 10 to 50 mg. daily; five patients more than 50 mg. but less than 100 mg.; and ten patients, 100 to 175 mg. daily to maintain satisfactory blood pressure levels.

Postural hypotensive effects were noted as early as seventy-two hours after an effective dose and became troublesome if the dose was rapidly increased. The response to even a small increment in dosage could not be predicted. For example, case 4, a patient with moderately severe hypertension, manifested relatively fixed blood pressure over a wide range of doses (Fig. 1); then, a 25 mg. increment in daily dose resulted in symptoms of postural hypotension. Case 2 (Fig. 2), a fifty-nine year old man with mild hypertension, had a minimal response to 5 mg. of guanethidine daily but severe postural hypotension developed when the dose was increased to only 10 mg. daily. The patient became very dizzy on standing, and the dose was reduced again at the seventh week to 5 mg. As the erect pressures began to rise another attempt to increase to 10 mg. daily at the tenth week was again followed by a severe drop in the erect pressure associated with syncope with essentially no change in the supine pressure. The erect pressures then rose slowly when the dose was decreased until a more marked increase in pressures occurred fairly rapidly between the seventeenth and nineteenth weeks. Dizziness on first arising in the morning and on standing was complained of by fourteen patients at some time during the course of treatment. In the majority of patients this was mild and was eliminated by lowering the dose. The action of the guanethidine was prolonged, a postural hypotensive effect being observed for periods up to five days after the drug was discontinued. Even more prolonged effects have been reported by others.[4]

The blood pressure changes at the end of the treatment period when taken in the recumbent position were not statistically significant. The mean systolic pressure dropped to 90.6 mm. Hg ± 12.5 per cent of the control values; the mean diastolic pressure dropped to 89.4 ± 9.2 per cent of the control values. The blood pressure changes when taken in the erect position were statistically significant. The mean systolic pressure was 77.6 ± 9.9 per cent of the control values; the mean diastolic pressure fell to 80.7 ± 10.7 per cent of the control values. The lowest erect blood pressure recorded during therapy was highly significant. The systolic pressure

TABLE I
Effects of Guanethidine on Twenty-Five Patients with Hypertension

Case No.	Age	Sex	Diagnosis	Known Duration of Hypertension (Years)	Blood Pressure before Therapy (mm. Hg)	Duration of Treatment (Weeks)
1	60	Female	HCVD†	13	180/106	15
2	59	Male	CP‡	6	160/100	14
3	58	Male	HCVD	6 months	220/140	12
4	57	Female	HCVD	10	210/140	19
5	58	Male	CP	5	180/120	8
6	58	Female	HCVD	15	195/100	12
7	54	Male	CP	4	185/125	16
8	46	Male	HCVD	...	230/150	28
9	55	Female	HCVD	9	210/120	14
10	49	Female	CP	13	260/160	15
11	63	Male	HCVD	4 months	220/130	17
12	71	Female	HCVD	20	200/100	12
13	31	Female	HCVD	2 months	186/130	8
14	60	Female	HCVD	2	220/100	8
15	64	Female	HCVD	2	218/116	10
16	49	Female	HCVD	1 month	185/116	12
17	73	Female	HCVD	4	294/112	12
18	57	Male	HCVD	2	230/130	8
19	37	Male	HCVD	3	180/115	9
20	59	Female	HCVD	4	180/117	11
21	44	Male	HCVD	2	180/108	9
22	34	Female	HCVD (toxemia)	3	180/112	11
23	54	Female	HCVD	10	160/118	8
24	65	Female	HCVD	6 months	235/120	13
25	48	Male	HCVD	3	170/120	6
Average	55	...	...	5.5	204/120	12

* In order to indicate the efficacy of guanethidine in reducing the blood pressure recorded in a standing position the lowest recorded value is included in the table. In many instances the symptoms accompanying the postural hypotension made it advisable to decrease the dose of guanethidine. This is reflected in the higher blood pressures recorded at the end of therapy. In some cases the recorded values do not reflect the maximum reduction in pressure because

was 71.3 mm. Hg ± 10.5 per cent of the control values and the diastolic pressure fell to 75.0 ± 9.1 per cent of the control values.

Toxic and Side Effects: The blood counts, liver and renal function tests enumerated previously were studied during the course of and at the end of treatment. The results were unaltered, indicating that the drug has no demonstrable toxic effects on the parameters studied. Roentgenograms of the chest and electrocardiograms obtained before and after treatment showed no essential change. In all cases the pulse rate fell an average of 16 to 20 beats per minute. In one patient with marked impairment of renal function the level of blood urea nitrogen rose in spite of cautious lowering of blood pressure. This later fell below the initial level, suggesting a renal hemodynamic readjustment. Further cautious lowering of blood pressure in this patient was then obtained. On the basis of this experience and that of Richardson and Wyso,[6] it appears that when impairment of renal function is marked, extreme caution must be exercised in the use of this drug to avoid renal decompensation. Gastrointestinal symptoms were relatively mild; nausea or vomiting occurred in four patients and diarrhea in two. No other side effects were noted. The accumulation of edema fluid during treatment with guanethidine has been previously described,[4] but this was not noted in the cases in our series.

TABLE 1 *Continued*

Final Daily Maintenance Dose of Guanethidine (mg.)	Blood Pressure at End of Treatment Period (mm. Hg)		Lowest Erect Blood Pressure* Recorded during Therapy (mm. Hg)	Toxic Effects
	Recumbent	Erect		
60	180/104	160/94	126/86	None
10	156/90	106/70	110/60	Dizziness
37.5	160/114	142/108	136/94	None
125	178/108	158/100	132/100	Nausea, diarrhea, dizziness
25	170/110	164/110	150/100	Dizziness
20	175/90	155/88	120/74	Dizziness
100	164/106	140/92	140/92	Nausea
75	210/130	170/94	136/84	Nausea
150	164/100	150/94	150/94	Dizziness
125	156/94	150/90	142/90	Dizziness
175	198/110	148/86	148/86	None
10	176/96	152/94	146/80	Nausea, dizziness
125	170/118	164/110	136/88	Dizziness
100	214/96	180/86	168/86	Diarrhea
75	186/96	146/84	150/86	None
75	180/110	158/110	158/100	Dizziness
37.5	280/125	220/108	140/70	Dizziness
75	180/120	176/112	144/90	Dizziness
75	150/95	140/95	140/95	None
25	180/110	155/95	150/85	Dizziness
50	170/105	150/100	140/95	None
150	180/105	140/100	140/100	Dizziness
50	205/115	160/100	160/100	None
100	180/100	140/80	140/80	Dizziness
50	180/115	160/110	140/105	None
80	182/106	155/96	143/89	...

the patients were advised to discontinue or reduce their medication if severe symptoms occurred. By the time of their visits to the outpatient clinic, the blood pressures recorded in the standing position had frequently increased to the point where symptoms were no longer present.

† HCVD = hypertensive cardiovascular disease; ‡ CP = chronic pyelonephritis.

COMMENTS

Mechanism of Action: Guanethidine manifests a definite hypotensive action. The mechanism of blood pressure reduction is incompletely understood but pharmacologic studies in the dog have indicated that the locus of action is probably at peripheral sympathetic receptor sites.

Burn and Rand[8] have suggested that "sympathomimetic amines may be divided into two classes," one class consisting of substances like norepinephrine, epinephrine and neosynephrine which act on vessel walls directly, causing a pressor response which is enhanced in animals pretreated with reserpine; the second group of substances, including tyramine, ephedrine and amphetamine, are ineffective in producing a vasopressor response in animals treated with reserpine. Since there is evidence that reserpine may deplete stores of norepinephrine in vessel walls, the first group of substances which act directly on the arteriolar wall is presumably more effective if the few receptor sites normally occupied by resting levels of norepinephrine are freed of this hormone by reserpine and can be stimulated anew. The second group of substances is thought to produce sympathomimetic effects by facilitating the release or action of norepinephrine at end organ sites. These substances cannot produce such effects if the wall is depleted of norepinephrine.

It has been similarly demonstrated by Page

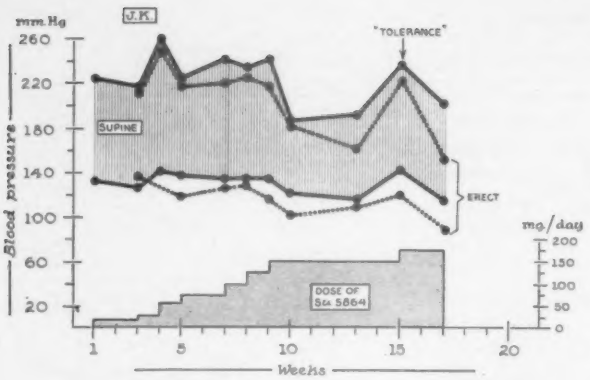

FIG. 3. This sixty-five year old man (Case 11) with moderately severe hypertension had a gradual fall in erect and supine pressures with increasing doses of guanethidine (first to tenth weeks).

and Dustan[4] that the pressor response to norepinephrine, angiotensin, vasopressin and metaraminol is augmented by prior administration of guanethidine and the response to tyramine, amphetamine, mephentermine and ephedrine is reduced. They have noted the resemblance of these effects to those described with reserpine and have further observed a reserpine-like quieting effect of intravenous guanethidine in dogs. It has been demonstrated also that although it abolishes the carotid sinus pressor reflex, guanethidine does not affect parasympathetic efferent transmission and postganglionic sympathetic action potentials. These observations have led previous investigators to conclude that the hypotensive action of guanethidine is similar to that of reserpine in blocking either the release, action or distribution of norepinephrine at peripheral sympathetic end organs.[3,4]

Hemodynamic Effects: With regard to the hemodynamic aspects of blood pressure reduction, Richardson and Wyso[6] observed that in some of their patients treated with guanethidine there was a reduction in glomerular filtration rate and renal plasma flow and a rise in blood urea nitrogen, especially if azotemia was present prior to treatment. These authors also noted a fall in cardiac output of about 10 per cent in the supine position and 20 per cent in the erect position, associated with reduction in blood pressures and attributed to venous pooling in the legs.

Development of Tolerance: Guanethidine has an advantage over the ganglionic blocking agents in that symptoms of constipation, dry mouth, urinary retention and pupillary changes are not observed. The optimum dosage of the drug, however, is difficult to ascertain because of marked individual variations in response. In all but mild degrees of hypertension, tolerance appears to develop to a dose which initially produced a satisfactory hypotensive effect, necessitating further increase in dosage. The development of such tolerance is illustrated by Case 11 (Fig. 3), a patient who had a satisfactory response to 150 mg. of guanethidine daily but gradually had an increase in blood pressure over the ensuing six weeks until a further increment in dosage was necessary. If the dose is increased rapidly, however, symptoms of postural hypotension become troublesome and slow gradual increases necessitate frequent visits to the outpatient clinic.

Clinical Applications: Because of the marked variation in the dose required for effective reduction of blood pressure, the unpredictability of an increment in dose, the severe postural hypotensive effect and the apparent development of tolerance, guanethidine seems to have little place in the treatment of patients with mild hypertension because more satisfactory drugs are available. Chlorothiazide, reserpine and their analogues have proved effective in lowering the pressure in this group of patients with relatively few serious side effects. Guanethidine seems to act similarly to reserpine but manifests a greater peripheral and relatively less central hypotensive effect. It would seem inadvisable to use guanethidine as the initial form of therapy in previously untreated patients with hypertension. It should probably not be used alone in therapy. The aforementioned regimen would eliminate the need for the ganglionic blocking agents in therapy. It would appear from our own experience and that of others that guanethidine has a role in the treatment of patients with more severe hypertension who do not respond to the rauwolfia derivatives and chlorothiazides alone. In the latter group it would seem advisable to add guanethidine in small and gradually increasing doses to the chlorothiazides instead of and occasionally in addition to reserpine.

It should be stated that because of the relatively small group of patients investigated, our views are to be considered tentative and may be subject to revision as larger series are studied. Studies are now in progress on the use of guanethidine in combination with other forms of antihypertensive therapy.

Summary

Twenty-five patients with chronic hypertension have been treated with guanethidine for periods ranging from six to eight weeks. The blood pressures fell an average of 22 mm. Hg systolic and 14 mm. Hg diastolic in the recumbent and 49 mm. Hg systolic and 24 mm. Hg diastolic in the erect position. The hypotensive action of the drug appears to be similar to that of reserpine in blocking either the release, action or distribution of norepinephrine at sympathetic end organs. The maintenance dose has ranged from 5 to 175 mg. daily; there has been marked variation between subjects in their response to a given dose. Occasionally tolerance seemed to develop. Postural hypotension was observed in all patients. Dizziness on standing was noted in fourteen patients, nausea or vomiting in four and diarrhea in two. Guanethidine has the advantage over the ganglionic blocking agents in that parasympatholytic effects are not observed.

It is concluded that guanethidine may be a useful supplement to other hypotensive agents but has little place in the treatment of hypertension when used alone.

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The Hypotensive Effects of Chlorothiazide and Hydrochlorothiazide

A Critical Comparison*

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A simple, practical method has been devised for evaluating the *relative* effectiveness of antihypertensive drugs already available as well as those undergoing clinical investigation. The recent upsurge of clinical interest in the hypotensive effect of the sulfonamide derivatives in hypertensive states of various etiologies[1–4] provided an opportunity to utilize this method of evaluation.

This report concerns a comparative study of the hypotensive effects of chlorothiazide and hydrochlorothiazide with and without reserpine in a group of seventy-eight ambulatory hypertensive patients. Reserpine was used for varying evaluation periods for six and a half years, chlorothiazide for three years and hydrochlorothiazide for two years. A large patient population initially observed during prolonged control and treatment periods with various antihypertensive agents was utilized. The data accumulated provide factual evidence of the relative effectiveness of the agents used.

Material

Seventy-eight ambulatory hypertensive patients were studied. These patients were followed from one to six years with multiple control periods of four to twenty-four months. During this time there were many periods of treatment with various antihypertensive drugs and drug combinations. The patients ranged in age from thirty-six to seventy-nine years with an average of fifty-eight (S.D. ± 10)† years. Forty-five were women and thirty-three were men. The known duration of hypertension was from one to twenty-six years with an average of 9.9 (±6.4) years.

The subjects were largely asymptomatic insofar as the so-called classical symptoms of hypertension were concerned (headache, dizziness, etc.). This lack of symptoms was characteristic of this particular hypertension clinic population. Approximately 10 per cent had manifestations of mild to moderate chronic congestive heart failure. A lesser percentage had a past history consistent with minor cerebrovascular accidents or myocardial infarcts. None had evidence of gross renal insufficiency, as judged by serial blood creatinine determinations and urine analyses.

The average blood pressure of the entire group of seventy-eight patients at the time of their initial visit to the hypertension clinic was 200 (±30) mm. Hg systolic and 111 (±15) mm. Hg diastolic. Following an average control period of five (±4) months the average blood pressure (designated as "final control" in Table I) was 191 (±30) mm. Hg systolic and 109 (±16) diastolic, representing a fall of 9 mm. Hg systolic and 2 mm. Hg diastolic, *preceding* initiation of specific therapy. Thus, as a group following control adaptation to clinic environment, these seventy-eight patients represented a stable hypertensive state.

Method

The blood pressures reported are the averages of the first nonresting recumbent values. Sitting and standing observations were recorded but are not included in this report. The final control values (Tables I and II) are the averages for the last clinic visit of seventy-eight patients (or smaller groupings from the total of seventy-eight) and are those of specific periods of treatment. Variation of blood pressure during the control period was determined by

† ± signifies 1 standard deviation (S.D.). "Significant" and "probably significant" as used in this paper are defined as p (probability) value of $p < 0.01$ and < 0.025, respectively.

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TABLE I

Average Blood Pressure Values (±1 S.D.) for Five Observation Periods with Three Groupings (A, B, C) of Long Term Hypertensive Patients

Factors	A	B		C	
	No Therapy	Chlorothiazide	Hydrochlorothiazide	Chlorothiazide and Reserpine	Hydrochlorothiazide and Reserpine
No. of patients	78	47	47	26	26
Age (yr.)	58 (±10)	58 (±5)	58 (±5)	59 (±13)	59 (±13)
Duration H.B.P. (yr.)	9.9 (±6.4)	10.5 (±6.8)	10.5 (±6.8)	12.1 (±7.5)	12.1 (±7.5)
Control period (mo.)	5 (±4)	4.5 (±3)	4.5 (±3)	4.7 (±3.4)	4.7 (±3.4)
Original B.P. (mm. Hg)	200/111 (±30/±15)	201/112 (±27/±17)	201/112 (±27/±17)	208/114 (±18/±20)	208/114 (±18/±20)
Prefinal control B.P.	187/108 (±33/±15)	185/109 (±31/±18)	185/109 (±27/±18)	200/112 (±30/±18)	200/112 (±30/±18)
Final control B.P.	191/109 (±30/±16)	189/109 (±31/±15)	189/109 (±31/±15)	192/109 (±31/±19)	192/109 (±31/±19)
Control B.P. change	3/1	4/0	4/0	8/3	8/3
Drug period B.P.	...	171/102 (±28/±13)	159/97 (±29/±15)	170/96 (±33/±17)	161/92 (±31/±15)
Drug change in B.P.	...	−18/−7	−30/−12	−22/−13	−31/−17
No. of patients without systolic reduction	...	13 (27%)	6 (13%)	5 (19%)	5 (19%)
No. of patients without diastolic reduction	...	17 (36%)	8 (17%)	2 (8%)	3 (12%)
Duration of treatment (mo.)	...	2.2 (±2.3)	1.8 (±0.4)	6.2 (±4.4)	2.3 (±2.9)

comparing the final control values described above with the average value recorded at the clinic prior to the last visit (designated as the "prefinal control" in Tables I and II).

The average periods of treatment ranged from one to twelve months. The blood pressure values representing the drug periods are averages of those of all patients, obtained at the last clinic visit while the patients were receiving a specific drug. The change in blood pressure for a drug period is the difference between the average for the reading of all patients of a specific grouping at the last clinic visit and the average of the final control value.

Chlorothiazide was administered in dosages of 250 mg. three times daily for periods of one to fifteen months; chlorothiazide-reserpine in doses of 250 mg. and 0.125 mg., respectively, three times a day for one to twelve months; hydrochlorothiazide 25 mg. three times daily for one to five months and hydrochlorothiazide-reserpine 25 mg. and 0.1 mg, respectively, three times daily for one to eight months.

If a hypotensive response occurred during a period of treatment the patients were thereafter placed on a control period during which a placebo was administered until the blood pressure returned to levels similar to those of the control. These subsidiary control periods ranged from one to three months in

TABLE II

Average Blood Pressure Values in Four Observation Periods with the Same Hypertensive Patients

Factors	Chlorothiazide	Chlorothiazide and Reserpine	Hydrochlorothiazide	Hydrochlorothiazide and Reserpine
Original B.P.	208/117	208/117	208/117	208/117
Prefinal control B.P.	194/113	194/113	194/113	194/113
Final control B.P.	190/111	190/111	190/111	190/111
Control change	4/2	4/2	4/2	4/2
Drug period B.P.	179/104	165/98	162/100	155/92
Drug change	−11/−7	−25/−13	−28/−11	−35/−19

duration. If no hypotensive response was noted, a control period was not interposed between periods of treatment.

Results

Control blood pressures are contained in Tables I and II. The variation between the average blood pressure recorded at the last visit (final control) and the previous visit (prefinal control) for the entire seventy-eight patients was 3 mm. Hg systolic and 1 mm. Hg diastolic. The greatest variation during the control period for special groupings of patients treated with a single drug or combination of drugs was 8 mm. Hg systolic and 3 mm. Hg diastolic.

Chlorothiazide versus Hydrochlorothiazide: Forty-seven patients were treated for comparable periods with chlorothiazide and hydrochlorothiazide (Table I). From an average control value of 189 (±31) mm. Hg systolic and 109 (±15) mm. Hg diastolic, a blood pressure reduction of 18 mm. Hg systolic and 7 mm. Hg diastolic was recorded with chlorothiazide and the reduction was 30 mm. Hg systolic and 12 mm. Hg diastolic with hydrochlorothiazide. Thus, the decrements showed a statistically significant reduction with both drugs. Hydrochlorothiazide, when statistically compared with chlorothiazide given to the same patients produced a greater statistically significant reduction in systolic blood pressure, but the difference in the average diastolic blood pressure was not statistically significant.

Chlorothiazide-Reserpine versus Hydrochlorothiazide-Reserpine: Twenty-six patients were evaluated with combinations of chlorothiazide-reserpine and hydrochlorothiazide-reserpine for periods of six and two months, respectively. These twenty-six patients were those who had not shown a definite response to either chlorothiazide or hydrochlorothiazide.

With chlorothiazide-reserpine, blood pressure reduction from a control value of 192 (±31) mm. Hg systolic and 109 (±19) mm. Hg diastolic in decrements of 22 mm. Hg systolic and 13 mm. Hg diastolic was noted. With hydrochlorothiazide-reserpine, the reduction was 31 mm. Hg systolic and 17 mm. Hg diastolic. The decrement in the average systolic blood pressure was statistically significant while that of the average diastolic blood pressure was probably of some significance (Table I).

The change in the average blood pressure with chlorothiazide-reserpine in this group of twenty-six patients was similar at the end of two months of treatment to that reported previously at the end of an average treatment period of six months.

Chlorothiazide versus Hydrochlorothiazide with and without Reserpine: Nineteen patients were evaluated during separate periods while receiving chlorothiazide alone, chlorothiazide with reserpine, hydrochlorothiazide alone and hydrochlorothiazide with reserpine (Table II). Thus, the blood pressure effects of each of these forms of therapy were evaluated relative to the same common baseline.

The average blood pressure values of these nineteen patients at their first clinic visit was 208 mm. Hg systolic and 117 mm. Hg diastolic. The change from the original to the final control value was a reduction of 18 mm. Hg systolic and 6 mm. Hg diastolic. The fluctuation between the final control and the prefinal control was 4 mm. Hg systolic and 2 mm. Hg diastolic. The reduction with chlorothiazide was 11 mm. Hg systolic and 7 mm. Hg diastolic; with chlorothiazide-reserpine, 25 mm. Hg systolic and 13 mm. Hg diastolic; with hydrochlorothiazide, 28 mm. Hg systolic and 11 mm. Hg diastolic; and with hydrochlorothiazide-reserpine 35 mm. Hg systolic and 19 mm. Hg diastolic. Thus, in these nineteen patients a significnt reduction in systolic pressure occurred with each drug singly and in combination while a probably significant diastolic decrement was observed.

Side Effects: Weight gains occurred in the majority of patients when reserpine was administered. The appetite-stimulating influence of reserpine was the outstanding effect encountered. In the patient with normal weight or obesity, this was considered undesirable. The discomfort of reserpine-induced nasal congestion was the second most frequent side effect. It was encountered in approximately 9 per cent of the patients treated with this drug. A similar observation was reported in a previous study from this clinic.[4]

Both chlorothiazide and hydrochlorothiazide produced symptoms of indigestion in a few patients. This effect was noted most frequently when the initial daily dose of the drug was large. However, when the drug was discontinued for a week and restarted in smaller amounts and gradually increased to a maximum of 750 mg. of chlorothiazide or 75 mg. of hydrochlorothiazide a day, indigestion reappeared less frequently. A nonspecific type of dermatitis de-

veloped in one patient with chlorothiazide and hydrochlorothiazide. No instance of hypokaliemia requiring replacement measures was encountered.

Comments

The data suggest that this technic serves as a reliable means for establishing the presence of hypotensive effect of the agents employed and also permits an accurate and practical means for comparing the relative antihypertensive qualities of such agents, singly or in combination.

Chlorothiazide alone in the stated dosage has a mild but definite hypotensive effect in hypertensive subjects which is augmented by the addition of reserpine whereas reserpine alone is not as effective.[5] The same patients first received chlorothiazide with or without reserpine and later hydrochlorothazide with or without reserpine. In the dosages employed hydrochlorothiazide therapy was accompanied by a greater hypotensive effect.

Twelve years ago Bryant and Blecha[6] reported the hypotensive effects of dietary sodium restriction. The natriuretic action of the sulfonamide drugs is well documented. Therefore, it is logical to postulate that these drugs may accomplish their hypotensive effect by the same mechanism, i.e., relative sodium depletion.

When the "-thiazides" were used, undesirable side effects were infrequent and, when present, were of a mild degree. Since a similar infrequency of side effects was not observed with reserpine, it is suggested that sulfonamide drugs be used initially in the treatment of hypertension.

Conclusions

1. Chlorothiazide and hydrochlorothiazide with and without reserpine demonstrate a statistically significant hypotensive effect.

2. Hydrochlorothiazide in doses of 75 mg. a day has a greater hypotensive effect than chlorothiazide in dosages of 750 mg. a day.

3. In a comparative study of nineteen patients, a significant reduction in systolic pressure and a possibly significant reduction in diastolic pressure accompanies the addition of reserpine to chlorothiazide and hydrochlorothiazide.

4. Observations with chlorothiazide for three years and hydrochlorothiazide for two years in the treatment of hypertension have demonstrated fewer side effects than noted with reserpine.

5. It is suggested that antihypertensive therapy be initiated with hydrochlorothiazide rather than reserpine and that reserpine be added only if satisfactory hypotensive effects are not achieved with hydrochlorothiazide alone.

6. Side effects, such as indigestion and electrolyte disturbances, that infrequently accompany "-thiazide" therapy are largely avoided when small initial doses are employed (i.e., 25 mg. hydrochlorothiazide a day) and gradually increased to maximal amounts.

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Clinical Observations on the Diuretic Effect of Hydrochlorothiazide*

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THIS paper reports our observations on the diuretic effect of hydrochlorothiazide† in patients with fluid retention and compares relative potency of this preparation with that of chlorothiazide.‡

CLINICAL MATERIAL AND METHODS

The effect of hydrochlorothiazide has been studied in a total of thirty-two patients, twenty-six from the clinic or ward population of the House of the Good Samaritan and six from the Cape Cod Hospital. Their ages ranged from five to seventy-six years with a mean of forty-four. Six were males and twenty-six were females. Table 1, listing patients according to diagnosis and cause of fluid retention, shows all but three patients had congestive heart failure.

The thirty-two patients were observed for a total of 2,741 patient-days with a mean of 85.7 days per patient. Within this observation period hydrochlorothiazide was administered for a total of 1,949 patient-days with a mean of 60.9 days per patient. The dose ranged from 25 to 200 mg. daily. Most patients received 100 to 150 mg. per day in divided doses.

Ambulatory Patients: Twenty-six patients were examined weekly on an out-patient basis to evaluate their congestive heart failure. Special forms recording history, physical findings and laboratory data were completed each time. In addition, each patient was asked to collect, measure and record the daily urine output on a specially prepared sheet. About half of the patients cooperated in this task with a high order of accuracy well corroborated by changes in weight. Body weight and average daily urine output, when available, were the chief measures of the degree of fluid retention.

Plan of Diuretic Administration: Because most of the ambulatory patients suffered from severe congestive failure and lived at some distance from the hospital, it was considered inadvisable to allow them even short periods without diuretics. Therefore, a comparison between periods on hydrochlorothiazide and diuretic-free periods could not be made. However, by substituting hydrochlorothiazide for other oral diuretics, which the patients were already taking, a comparison could be made between hydrochlorothiazide and the other oral diuretics and a dose-relationship could be established. To make this comparison observations on body weight and other data were recorded for consecutive weekly periods, and diuretics were administered as follows:

1. In the first one-week period patients continued on their customary regimen, which in all cases included an oral diuretic. This week was designated the base-period.
2. If the regimen of the base-period included chlorothiazide, during the second period hydrochlorothiazide was substituted in one-tenth the amount without changing any other medication. If some oral diuretic other than chlorothiazide (such as ammonium chloride or acetazolamide) had been given during the base-period, hydrochlorothiazide in a dose of 100 mg. per day was substituted during the second period.
3. During the third period the dose of hydrochlorothiazide was either increased or decreased according to the diuretic response in the second period.
4. During subsequent periods further adjustments were often made in the dose of hydrochlorothiazide to obtain the optimum dose. At no time, however, was the daily amount of this preparation allowed to exceed 200 mg. Also during subsequent periods some patients on chlorothiazide during the base-period were again given this diuretic for further comparisons between it and its analog.

Thus, seventy-three comparisons of hydrochlorothiazide with chlorothiazide were possible in twenty patients. In addition, limited data were obtained in four patients taking ammonium chloride and in two patients on acetazolamide during the base period.

Other Medication: At the beginning all twenty-six

† Supplied by Merck, Sharp & Dohme as Hydrodiuril.®

‡ Supplied by Merck, Sharp & Dohme as Diuril.®

* From the House of the Good Samaritan, Children's Hospital Medical Center, and the Department of Pediatrics, Harvard Medical School, Boston, Massachusetts, and the Cape Cod Hospital, Hyannis, Massachusetts. This study was supported by a grant from the Merck, Sharp and Dohme Research Laboratories.

TABLE I

Distribution of Patients by Diagnosis and Cause of Fluid Retention

Diagnosis	No. of Patients
Congestive heart failure	29
Rheumatic valvular disease	23
Arteriosclerotic heart disease	5
Hypertensive heart disease	1
Edema secondary to high dosage steroid therapy	2
Lupus erythematosus with renal involvement	1
Total	32

ambulatory patients took digitalis; six received mercurial diuretics by intramuscular injection in addition to oral diuretics; and all but two were given supplementary potassium in the form of potassium chloride or orange juice. The dose of these medications remained constant during the base-period and subsequent periods when hydrochlorothiazide was compared with chlorothiazide or other oral diuretics. After the comparisons were completed, an attempt was made to decrease the dose of the mercurial diuretics, digitalis and potassium and to omit these drugs entirely in some cases.

Ward Patients: Six ward patients with fluid retention could not be included in the study plan used for the twenty-six ambulatory patients but they were carefully observed and provided supplementary clinical data on the diuretic effect of hydrochlorothiazide. Three had rheumatic heart disease with severe congestive failure; two had fluid retention secondary to adrenocortical steroid therapy for rheumatic fever; and one had lupus erythematosus with renal damage and fluid retention.

RESULTS

Among the three ward patients with rheumatic heart disease and severe congestive failure the diuretic response to hydrochlorothiazide was excellent in two and very poor in one. One patient with an excellent response was a twenty-three year old female who, in spite of full digitalization, had considerable edema, hepatic congestion and other signs of heart failure on admission to the House of the Good Samaritan. A single 2 cc. injection of a mercurial diuretic produced an 1,850 cc. urine output and a $4^1/_2$ pound loss of weight within twenty-four hours. However, over the next three days she voided only an average of 615 cc. per day and her weight began to increase. Hydrochlorothiazide, 150 mg. per day, was added to her regimen on the fourth day, and during the next nine days that she took this drug the average daily urinary output increased to 1,640 cc. Within the first three days of hydrochlorothiazide therapy she lost six pounds and reached a stable dry weight. The second patient, an eleven year old boy, required mercurial diuretic injections every three days to control his severe right-sided heart failure. Substitution of 150 mg. of hydrochlorothiazide daily for the mercurial injections controlled equally well all signs of congestive failure. The third patient was refractory to hydrochlorothiazide in doses up to 200 mg. per day. She was a twenty-seven year old female with far advanced valvular disease and so-called intractable edema, which had failed to respond previously to other diuretics, including intramuscular mercurial preparations.

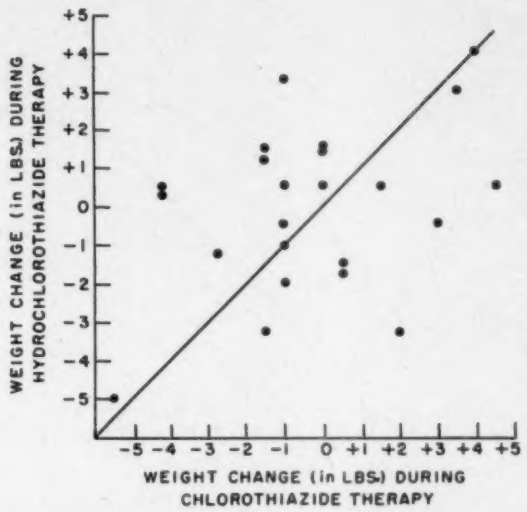

FIG. 1. Change in weight during 100 mg. per day of hydrochlorothiazide plotted against change in weight during administration of 1,000 mg. per day of chlorothiazide. Each drug given for one week. Total of twenty-three comparisons in twelve patients.

A marked diuretic effect occurred in one of the two cases of edema associated with the administration of adrenocortical steroids. This patient, a seven year old girl, lost twelve pounds within three days during which 50 mg. of hydrochlorothiazide per day were given. In the other case the diuretic effect was good but less dramatic. The sixth ward patient, a sixteen year old girl with disseminated lupus erythematosus, renal involvement, edema, and serum nonprotein nitrogen of 100 mg. per cent, showed no demonstrable diuretic effect.

Comparison of Hydrochlorothiazide with Chlorothiazide: Data for this comparison came from observations on twenty of the twenty-six am-

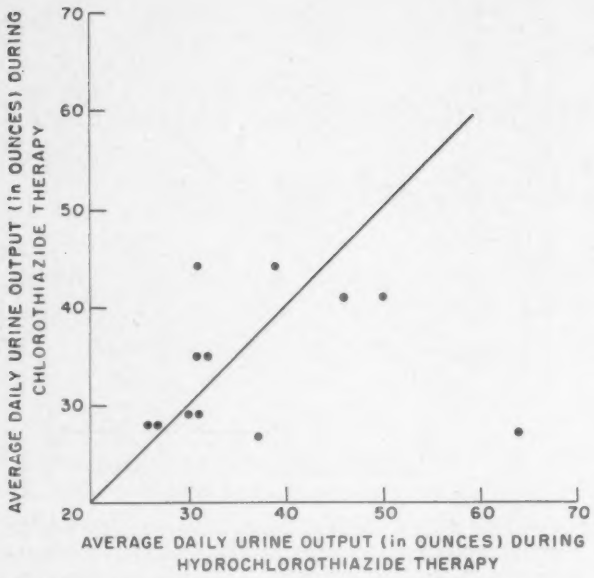

FIG. 2. Average daily urine output during 100 mg. per day of hydrochlorothiazide plotted against average daily urine output during administration of 1,000 mg. per day of chlorothiazide. Each drug given for one week. Total of twelve comparisons in six patients.

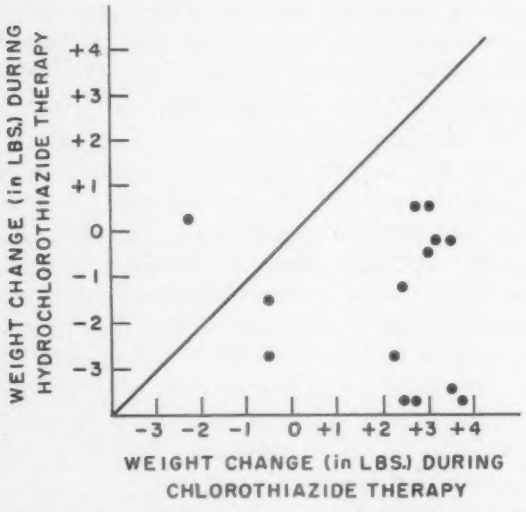

FIG. 3. Change in weight during administration of 150 mg. per day of hydrochlorothiazide plotted against 1,500 mg. per day of chlorothiazide. Each drug given for one week. Total of fourteen comparisons in four patients.

bulatory patients with congestive heart failure who were studied according to the plan previously described and who received chlorothiazide as an oral diuretic in the base period. These twenty patients provided a total of seventy-three comparisons in regard to changes in weight and average daily urine output (Figs. 1 to 5).

The scattergraph in Figure 1 shows the data from twenty-three comparisons of changes in

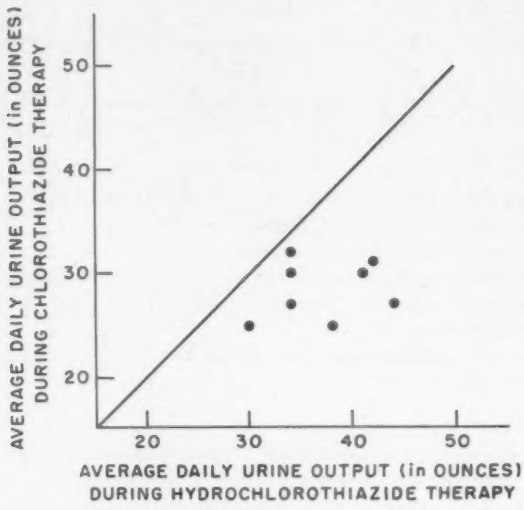

FIG. 4. Average daily urine output during administration of 150 mg. per day of hydrochlorothiazide plotted against average daily urine output during 1,500 mg. per day of chlorothiazide. Each drug given for one week. Total of eight comparisons in four patients.

weight in twelve patients, all of whom received 1,000 mg. per day of chlorothiazide in one weekly period and 100 mg. per day of hydrochlorothiazide in another weekly period. In some comparisons the period of chlorothiazide treatment preceded, while in others it followed the period of treatment with hydrochlorothiazide. The weight change during the chlorothiazide period is shown on the abscissa and that during the corresponding hydrochlorothiazide period on the ordinate. The resulting plotted point for each comparison demonstrates whether the diuretic effect of chlorothiazide or that of hydrochlorothiazide was greater. In those instances in which the plotted points fall below the line of equal response (the diagonal line bisecting the 90 degree angle made by the abscissa and the ordinate), the diuretic effect of hydrochlorothiazide was the greater. When the plotted points fall above the diagonal line, the diuretic effect of chlorothiazide was the greater. It is evident from inspection of the scattergraph that the plotted points are more or less equally distributed around the diagonal line and, therefore, that in these particular twenty-three comparisons the diuretic effect of 100 mg. of hydrochlorothiazide was approximately the same as that of 1,000 mg. of chlorothiazide.

Twelve of the twenty-three pairs of periods utilized for comparing the changes in weight in Figure 1 could also be used for comparing the average daily urine output. These data con-

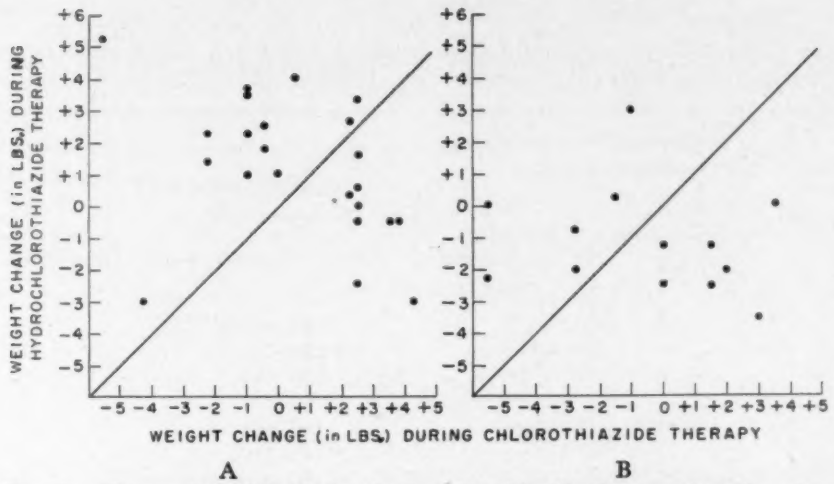

FIG. 5. Change in weight during hydrochlorothiazide therapy plotted against change in weight during chlorothiazide therapy, when each drug was given for one week. A, ratio of daily dose of hydrochlorothiazide to chlorothiazide is less than 1 : 10. Total of twenty-three comparisons in eight patients. B, ratio of daily dose of hydrochlorothiazide to chlorothiazide is more than 1 : 10. Total of thirteen comparisons in five patients.

cerning fluid output were obtained from seven patients who collected and measured reliably the amount of urine voided each day. The scattergraph of Figure 2, comparing the average daily urinary outputs, resembles that of Figure 1 and confirms the conclusion that in these patients 100 mg. of hydrochlorothiazide had a diuretic effect approximately equal to that of 1,000 mg. of chlorothiazide. It is to be noted that, when urinary output is plotted, the data for hydrochlorothiazide are shown on the abscissa and the data for chlorothiazide on the ordinate.

Four patients provided fourteen comparisons of the effects on body weight of hydrochlorothiazide and chlorothiazide when the two preparations were given in daily doses of 150 mg. and 1,500 mg., respectively (Fig. 3), and eight comparisons of average daily urinary output (Fig. 4). From the distribution of the plotted points in Figures 3 and 4 it is evident that in these particular four patients 150 mg. of hydrochlorothiazide proved to have a greater diuretic effect than 1,500 mg. of chlorothiazide even though the dosage ratio of 1:10 for the two preparations was the same as that for the comparisons shown in Figures 1 and 2.

In all of the comparisons in Figures 1 to 4 the ratio of hydrochlorothiazide to chlorothiazide was 1 : 10. In contrast, Figure 5 provides comparisons when the daily dosage ratios of the two diuretics were less than 1 : 10 (scattergraph A), and greater than 1 : 10 (scattergraph B). Thus, in scattergraph A the effect on weight of 50 or 75 mg. per day of hydrochlorothiazide has been compared with that of 1,000 mg. of chlorothiazide per day, or the effect of 100 or 125 mg. per day of hydrochlorothiazide has been compared with the effect of 1,500 mg. of chlorothiazide per day. In scattergraph B the effect on weight of 125 or 150 mg. of hydrochlorothiazide per day has been compared with that of 1,000 mg. of chlorothiazide per day. The more or less equal distribution of the plotted points in both scattergraphs of Figure 5 indicates that under one set of circumstances hydrochlorothiazide in an amount less than one-tenth that of chlorothiazide produced a diuretic response equal to the response of the latter preparation; whereas under another set of circumstances an amount of hydrochlorothiazide more than one-tenth the amount of chlorothiazide was required to produce a comparable response.

Comparison of Hydrochlorothiazide with Other Diuretics: Two clinic patients receiving 375 and 1,000 mg. of acetazolamide daily at the inception of the study continued with this medication during the base period. When hydrochlorothiazide was substituted subsequently, it appeared to give at least an equally good diuretic response in doses from 100 mg. to as little as 50 mg. per day.

Four of the ambulatory patients had been taking 3.0 to 4.0 gm. of ammonium chloride per day during the base period. In two of these, who were also being given intramuscular injections of a mercurial diuretic, substitution

TABLE II

Results of 101 Serum Chloride Determinations during Therapy with Chlorothiazide or Hydrochlorothiazide

Concentration of Chloride (mEq./L.)	Number of Determinations during Therapy	
	Chlorothiazide	Hydrochlorothiazide
84 or less	0	1
85–89	1	2
90–94	6	18
95–99	5	33
100–106*	11	23
107 or greater	1	0
Total	24	77

* Normal range.

TABLE III

Results of 101 Serum Sodium Determinations during Therapy with Chlorothiazide or Hydrochlorothiazide

Concentration of Sodium (mEq./L.)	Number of Determinations during Therapy	
	Chlorothiazide	Hydrochlorothiazide
124 or less	0	0
125–129	0	3
130–134	6	11
135–137	7	23
138–144*	10	36
145–149	1	4
150 or greater	0	0
Total	24	77

* Normal range.

of hydrochlorothiazide for the ammonium chloride increased diuresis. In the two patients whose only diuretic during the base period was ammonium chloride, the substitution of 100 mg. per day of hydrochlorothiazide increased urinary output and later controlled their congestive failure with as little as 25 mg. per day.

The twenty-six ambulatory patients receiving various oral diuretics at the inception of the study included six patients who also required supplementary injections of a mercurial preparation. Four of these six were among the twenty patients who had been taking oral chlorothiazide at the beginning of the study and during the base period while two were included in the group of four patients who had been taking ammonium chloride. In three of the four patients receiving chlorothiazide the substitution of hydrochlorothiazide allowed for a reduction in the dose of mercurial diuretics by 25 to 50 per cent, and in one of the two patients receiving ammonium chloride during the base period the injections of mercurial diuretic could be completely discontinued when hydrochlorothiazide was given.

Effect on Blood Pressure and Heart Rate: Seventeen of the twenty clinic patients receiving chlorothiazide during the base period had no change in systolic blood pressure or, at the most, a decrease of less than 10 mm. Hg. In two patients the systolic pressure fell 10 to 15 mm. Hg. One patient (the only one with hypertension) showed a drop in blood pressure from a mean of 180/105 to a mean of 150/95 mm. Hg when hydrochlorothiazide was substituted for chlorothiazide.

The remaining twelve ward and clinic patients, who previously had not been given chlorothiazide, were normotensive at the beginning of hydrochlorothiazide administration. When the latter drug was given, the systolic pressure remained the same or decreased by less than 10 mm. Hg in five patients and decreased 10 to 15 mm. Hg in six patients. In the remaining subject, a clinic patient receiving acetozolamide during the base period, the blood pressure dropped from a mean of 130/65 to a mean of 110/65 mm. Hg.

Except for the hypertensive patient there was no instance in which the diastolic blood pressure decreased by as much as 10 mm. Hg.

A definite slowing of the heart rate during hydrochlorothiazide therapy was repeatedly observed in ten of eighteen patients who had atrial fibrillation and were taking digitalis. The average heart rate for the group showing this phenomenon was 73 beats per minute prior to hydrochlorothiazide and 59 beats per minute during treatment with this diuretic. In four patients whose heart rates decreased to between 43 and 52 beats per minute, it was necessary to discontinue digitalis and/or hydrochlorothiazide for varying periods. Later, three of these patients could be maintained on lower digitalis dosage as long as hydrochlorothiazide was continued. This apparent slowing effect of hydrochlorothiazide was observed even though the initial heart rates in all ten patients were recorded during chlorothiazide medication.

Effect on Serum Electrolytes: A total of 101

TABLE IV

Results of Ninety-Two Serum Potassium Determinations during Therapy with Chlorothiazide and Hydrochlorothiazide with and without Supplementary Potassium

Concentration of Potassium (mEq./L.)	Number of Determinations during Therapy		
	Chlorothiazide with Suppl. Potassium	Hydrochlorothiazide with Suppl. Potassium	Hydrochlorothiazide without Suppl. Potassium
2.4 or less	0	0	0
2.5–2.9	0	0	1
3.0–3.4	4	13	1
3.5–3.9*	6	21	9
4.0–4.4*	8	15	2
4.5–4.9*	1	4	2
5.0–5.4*	1	3	0
5.5–5.9*	0	1	0
6.0 or greater†	0	0	0
Total	20	57	15

* Within normal range.

† Not recorded are six elevated levels of potassium due to hemolysis of the blood specimen.

TABLE V

Incidence and Types of Untoward Effects in Thirty-Two Patients Receiving Hydrochlorothiazide

Type of Effect	Instances	No. of Patients
Side effects		10
Fatigue	4	
Nausea	1	
Drowsiness	4	
Dizziness	2	
Dryness of mouth	3	
Myalgia	2	
Abdominal cramps	1	
Urticaria*	1	
Subcutaneous petechiae*	1	
No side effects		22
Total		32

* There is some question whether these manifestations were related to hydrochlorothiazide.

serum electrolyte determinations were made in nineteen patients with congestive heart failure (Tables II, III and IV). The distribution of the serum chloride concentrations was approximately the same during treatment with hydrochlorothiazide as during treatment with chlorothiazide. In general the chloride concentrations tended to be somewhat low, 50 to 70 per cent of them being under the normal range (Table II). As with the chlorides the distribution of sodium concentrations observed during hydrochlorothiazide therapy paralleled that during chlorothiazide therapy, and the level of sodium often was found to be slightly low (Table III).

No striking difference was noted between the distribution of potassium levels during hydrochlorothiazide and chlorothiazide therapy (Table IV). Furthermore, even the omission of supplementary potassium did not have an appreciable influence on the levels. The only instance of a potassium concentration below 3 mEq./L. was observed in a patient treated with hydrochlorothiazide without supplementary potassium. At the time of the determination, which revealed a concentration of 2.7 mEq./L., there was also clinical evidence of hypokalemia.

Untoward Effects: Of the thirty-two patients in the entire series, twenty-two had no untoward effects, while the remaining ten patients reported one or more complaints (Table V). In two patients who had a brisk diuretic response while not taking supplementary potassium, weakness, dryness of the mouth, and muscle pains were sufficiently distressing to cause some degree of incapacitation. However, moderate reduction of the dose of hydrochlorothiazide together with the administration of orange juice in one patient and reduction of the dose alone in the other patient completely alleviated these symptoms without diminishing the diuretic response. One of these two patients had a serum potassium level of only 2.7 mEq./L. In the other patient, whose symptoms also suggested hypokalemia, it was not possible to obtain a blood specimen at the time of symptoms. In the remaining eight patients with complaints the symptoms were so mild that it was not necessary to modify their medication.

COMMENTS

Our data indicate that hydrochlorothiazide is a potent diuretic agent. In only two of the thirty-two patients was it impossible to control fluid retention adequately. One of the poor results was in a patient with severe congestive heart failure who previously had showed no response to other oral and intramuscular diuretics. The second therapeutic failure was a patient with disseminated lupus erythematosus and severe renal involvement. The lack of response of this patient suggests that severe kidney damage may interfere with the action of hydrochlorothiazide. Similar findings have been reported with chlorothiazide.[1,2] The diuretic response of two patients with fluid

retention secondary to corticosteroid administration suggests that hydrochlorothiazide may control this condition.

From our data it may be concluded also that the relative amounts of hydrochlorothiazide and chlorothiazide required to give the same diuretic effect is generally 1 : 10. Although this conclusion is consistent with the results of preclinical experiments in dogs[3] and with the majority of clinical reports concerned with the use of these two preparations in man,[4,5] our data suggest that there are variations in response among subjects so that this ratio may be as little as 0.5 : 10 or as great as 2 : 10.

The relatively few patients in this series who had been receiving injections of mercurial preparations prior to the use of hydrochlorothiazide do not allow for an accurate comparison of these two diuretics.

Although hydrochlorothiazide is useful in the treatment of hypertension, no normotensive patients showed an appreciable decrease in blood pressure, and the slight decrease in some cases caused no symptoms. It can be concluded that hydrochlorothiazide can be given to patients with congestive heart failure and normal blood pressure without any risk of marked hypotensive effect.

The bradycardia in ten patients also taking digitalis needs special emphasis, since this effect of hydrochlorothiazide has not been stressed elsewhere. It would seem that this slowing effect was related to hydrochlorothiazide administration since all these patients had been taking digitalis for many years in their established maintenance dose without showing extreme bradycardia and because withdrawal of hydrochlorothiazide alone restored the usual heart rate.

Our results suggest that hydrochlorothiazide influences the sodium, chloride and potassium level of the blood serum approximately the same as chlorothiazide. Some investigators[6] have found hydrochlorothiazide affects potassium excretion less than chlorothiazide; from the limited number of cases in our study this observation could not be confirmed. The sodium and chloride depletion was never enough to produce symptoms, and only two patients had complaints which could be related to potassium depletion. Both patients were without supplementary potassium. In one the serum potassium level decreased to 2.7 mEq./L.; in the other it was not possible to obtain a blood specimen at the time of symptoms. Since our experience with probable hypokalemia was limited to these two patients and since none of the patients receiving supplementary potassium had symptoms of potassium loss, it would seem advisable to provide supplementary potassium in some form for every patient taking hydrochlorothiazide. Untoward effects, except for the two instances that were probably related to hypokalemia, were infrequent and so mild that there was no need for change in medication.

Our experience with hydrochlorothiazide during this study and our previous experience with chlorothiazide suggest both drugs have similar diuretic and other clinical effects and differ only in dosage.

Summary and Conclusions

1. Hydrochlorothiazide, an analog of chlorothiazide, has been studied for its diuretic effect in thirty-two patients with fluid retention. In twenty patients its effects were compared with those of the parent compound, chlorothiazide.

2. In the therapeutic dosage range the ratio of hydrochlorothiazide to chlorothiazide is approximately 1 : 10, but there are some individual variations concerning this proportion.

3. Hydrochlorothiazide is a very potent oral diuretic agent which sometimes allows significant reduction in mercurial diuretics or complete replacement of these drugs.

4. Untoward effects in only ten of thirty-two patients were generally mild. In two cases with more severe symptoms these symptoms appeared related to an abundant diuretic effect rather than to any toxicity of the hydrochlorothiazide. The administration of supplementary potassium may help reduce untoward effects.

5. Bradycardia associated with hydrochlorothiazide administration was noted in ten patients with atrial fibrillation who were also taking digitalis. In some cases the maintenance dose of digitalis could be reduced.

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Effect of Reserpine and Syrosingopine on the Rate and Contractility of the Human Heart*

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ONE OF THE most conspicuous effects of the rauwolfia drugs is a reduction of the heart rate. This phenomenon has been ascertained in experimental animals,[1–5] as well as in normal human subjects[6] and patients.[6–15]

It proved particularly impressive in cases of abnormal cardiac acceleration connected with mitral valvular lesions,[6,7,14] chronic cor pulmonale,[7,14] "hypertensive heart disease,"[10,15] coronary heart disease including the postinfarction syndrome,[6,14] atrial fibrillation,[7,13] paroxysmal tachycardia,[8,9] thyrotoxicosis[7] and "neurotachycardia."[7]

Albano and Motta[7] observed striking reductions of pulse rate from an average of 128 to an average of 75 beats per minute in thirty-eight patients, using an initial dosage of 1 mg. reserpine per day intravenously for four to six days followed by an oral dosage of 0.25 mg. two to three times daily. Schumann and Rehberg,[14] by administering reserpine to seventy-three patients in a dosage of 0.25 mg. twice daily, achieved an average fall from 85 to 68 beats per minute with a maximum drop from 145 to 65. Marangoni and Cavusoglu[13] found a "loading dose" of 0.75 mg. of reserpine daily for three days and a maintenance dose of 0.25 to 0.5 mg. successful in slowing the ventricular rate in twelve of sixteen patients with atrial fibrillation.

Improvements of abnormal electrocardiograms (elevation of S-T segment and restoration of a positive T wave) were observed by several investigators.[11,14,16] Clinically beneficial effects concerned anginal symptoms[12,14] as well as manifestations of congestive heart failure,[6,14] the latter by permitting a reduction of digitalis glycosides or even by replacing them. The influence of reserpine in lowering the blood pressure proved, in general, less consistent and less marked than in reducing the heart rate.[7,14]

A reduction of central nervous system sympathetic stimuli was suspected by Bein[1,17] and Windsor[18] to be involved in the bradycardic effect of the rauwolfia drugs but Vogt[19] failed to detect a diminution of electrical impulses in the preganglionic sympathetic fibers and thus questioned the participation of a central sympathoinhibitory mechanism. Brodie et al.[20] observed augmented parasympathetic discharges from the central nervous system under the influence of rauwolfia drugs. However, neither the cardioinhibitory nor the metabolic actions of these drugs on the heart muscle[7,12] were abolished by atropine.[7,15]

The discovery by Bertler, Carlsson and Rosengren[21] that reserpine depletes the catecholamine stores of the heart, subsequently confirmed by others,[3,22–24] made it appear likely that these local losses of sympathomimetic amines are largely responsible for the characteristic effects of rauwolfia on the heart such as the following: bradycardia, prolongation of diastole[14] and of atrioventricular conduction,[25] depression of the contractile amplitude,[22] increase of myocardial glycogen,[7] reduction of epinephrine-induced myocardial glycogen losses[12] and a normalization of "hypoxic" changes of the electrocardiogram.[11,14,16] In view of the "key position of the catecholamines in cardiovascular pathology"[26] the reported favorable responses in angina pectoris[12,14] and in congestive heart failure[6,14] may be understood on the same basis.

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Two complicating factors must be taken into consideration in interpreting the cardiovascular effects of rauwolfia drugs: (1) initial "loading" or "challenging" doses are prone to elicit adrenergic reactions diametrically opposed to later long-range effects because of the sudden liberation and activity of physiologically stored catecholamines before they are enzymatically destroyed and before depletion becomes functionally effective;[6,27-29] (2) catecholamine-depleted tissues are hypersensitive to whatever quantities of catecholamines reach them from other intra- or extracorporeal sources[1,3,22,30] so that the resulting functional state represents a compromise between an adrenergic-weakening (depletion) and an adrenergic-exaggerating (hypersensitivity) element, respectively.

A more recently introduced synthetic rauwolfia compound, syrosingopine (Singoserp®), shares with reserpine its catecholamine-depleting and corresponding pharmacodynamic effects on the cardiovascular system (vasodepression and bradycardia[3,4]) but differs from it in leaving the catecholamine stores of the brain more or less intact,[3] and in being accordingly free of sedating and mentally depressing side effects.[4]

Absolute sympathetic adrenergic overactivity[26] or a relative adrenergic preponderance due to a deficiency of cholinergic sympathoinhibitory mechanisms[31] constitute a major contributory factor in the pathogenesis of functional and degenerative heart diseases and the cardiac action of the rauwolfia drugs mimics the effects of bilateral sympathectomy;[22] therefore, these drugs command a great deal of interest both theoretically and from the point of view of cardiac prophylaxis and therapy. For this reason we decided to study the action of reserpine and syrosingopine on the cardiac dynamic cycle in correlation with heart rate and blood pressure at different dosage levels, and the effect of reserpine on the cardiac chronotropic response to exercise without and with elimination of vagal effects by atropine.

Data concerning the effect of reserpine on the dynamics of the human heart were presented by Lasch and Theinl[6] in 1957. These authors limited their observations to one to two hours after the intravenous injection of 1 to 3 mg. of reserpine and noted the following: (1) slight decrease of the blood pressure; (2) slowing of the heart rate which was most marked in instances of an initial rapid pulse; (3) transient augmentation of stroke volume and cardiac output in twelve out of twenty tests, lasting up to eighty minutes and followed by a decrease; (4) prolongation of diastole; (5) shortening of the isometric (tension) period of systole in half of the tests; and (6) no alteration of the isotonic (ejection) period of systole. At the time when these investigations were carried out, neither the catecholamine-depleting properties of the rauwolfia drugs nor the differences between early ("loading") and subsequent maintenance effects were known. This also applies to our first short-range experiments with intravenous injection of large doses.

In all our experiments with exception of the exercise tests the dynamic cycle of the left ventricle (total systole, isometric and isotonic periods, "chronodynogram") was measured, particularly because the isometric (tension) period is a sensitive indicator of neurovegetative inotropic influences upon left ventricular activity. The isometric period is shortened by adrenergic and lengthened by vagal and/or sympathoinhibitory mechanisms.[31,32] Chronotropic and inotropic reactions of the heart although directionally coordinated[1] as a rule occur independently from each other due to their separate origin in the sinus area and the ventricular musculature respectively. Hence, their measurements provide direct information concerning basically different parameters of cardiac function.

Material and Methods

All tests were carried out before breakfast and after an appropriate resting period in quiet surroundings. None of the test subjects presented any evidence of organic cardiovascular pathology.

The "chronodynogram" (measurement of the phases of the left ventricular dynamic cycle) was recorded according to the method of Blumberger[33] as described elsewhere.*[32] Day to day comparisons of blood pressure, heart rate and chronodynogram data were based on the medium of control readings, obtained on three pre-experiment days.

* Electrocardiogram (lead II), phonocardiogram over the left side of the upper sternum, and the carotid pulse wave were recorded simultaneously with a paper speed of 10 cm. per second. The distance from the beginning of Q (or R, if no Q was present) to the first vibration of the second heart sound corresponds to the length of the total systole. The isotonic (or ejection) period extends from the beginning of the steep ascent of the carotid pulse wave to the bottom of its "incisura." Subtraction of this dimension from that of the total systole (all expressed in thousandths of a second) yields the length of the total isometric contraction (or tension) period. Each measurement reported here represents an average of the readings obtained from ten to twenty individual cardiac cycles.

TABLE I
Results of Tests during Acute Phase in Eight Subjects

Case No.	Sex	Age (yr.)	Reserpine Intravenous (mg.)	Hours Between Injection and Second Test	Blood Pressure (mm. Hg)				Heart Rate		Isometric Period (TP)*		Isotonic Period*	
					Systolic		Diastolic							
					Before Injection	Δ	Before Injection	Δ	Before Injection	Δ	Before Injection	Δ	Before Injection	Δ
1	M	25	5	5	128	−13	70	−23	64	+16	73	+4	299	−13
2	M	50	10	5	143	−20	78	−9	82	−24	106	−12	237	+57
3	F	17	10	5	118	−15	55	−13	102	−43	78	±0	258	+64
4	F	36	10	4	103	−5	63	−8	91	−31	91	−5	273	+30
5	M	25	10	6	110	−7	60	−24	59	−6	74	−12	295	+37
6	F	16	10	4	124	−13	68	−18	58	−3	93	+11	316	+8
7	F	51	10	5	106	−7	69	−1	91	+2	55	−3	261	+11
8	M	27	10	5	102	−4	74	−28	57	+3	72	+9	328	−20
Average		31	9.4	5	117	−11	67	−16	75	−11	80	−8	283	+22

* Expressed in thousandths of a second.

Exercise tests were carried out on a treadmill (speed: four miles per hour for five minutes). Heart rates during exercise periods were determined by recording the electrocardiogram during the last fifteen seconds of each minute while the subjects were standing still; subsequently, in recumbent position for fifteen more minutes. Some of the heart rate curves during exercise periods are averages of two to three successive, identically performed, tests.

In the acute loading experiments, reserpine (Serpasil®) was administered intravenously in a dosage range used by psychiatrists for sedation (5 to 10 mg.),[34] and with a follow-up of only four to six hours. Long range medication with reserpine (0.1 to 0.2 mg. per day) and syrosingopine (2 to 4 mg. per day) was started after three control tests and continued for weeks and months. Atropine sulfate was injected intravenously in a dosage of 0.025 mg. per kg. body weight.

RESULTS

Tests during Acute Phase with Large Doses: In eight subjects intravenous injection of 5 to 10 mg. of reserpine was followed by diminution

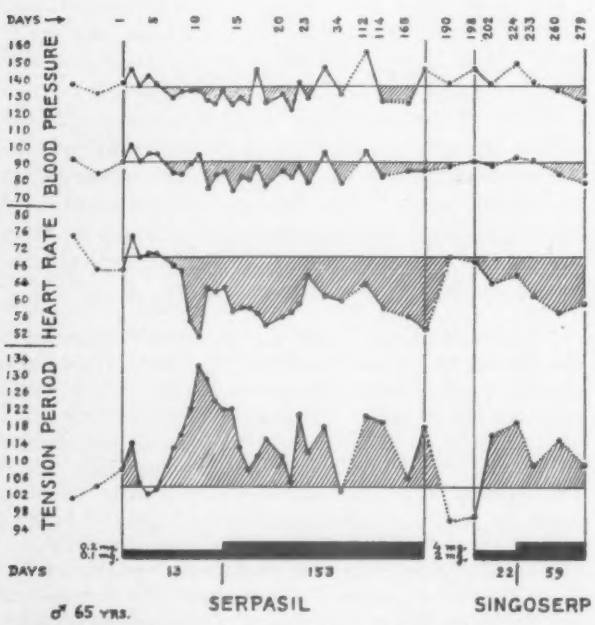

FIG. 1. Influence of reserpine and syrosingopine on blood pressure, heart rate and isometric (tension) period of left ventricle. (Case 9.)

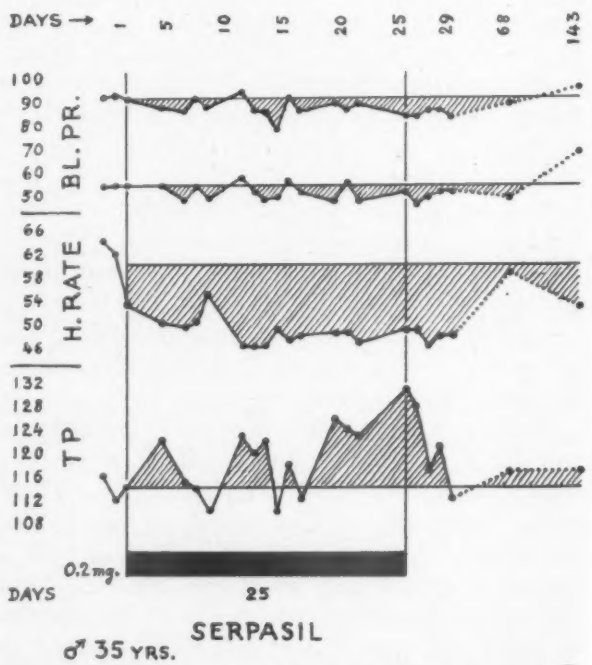

FIG. 2. Influence of reserpine on blood pressure, heart rate and isometric (tension) period of left ventricle. (Case 10.)

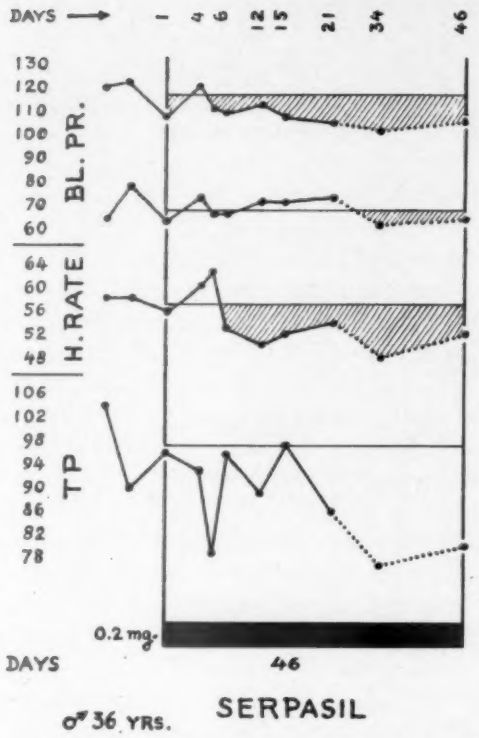

FIG. 3. Influence of reserpine on blood pressure, heart rate and isometric (tension) period of left ventricle. (Case 11.)

of the blood pressure and in five instances by a reduction of the heart rate, of widely varying degrees (Table 1). The isometric or tension period was erratic, showing about equal length-

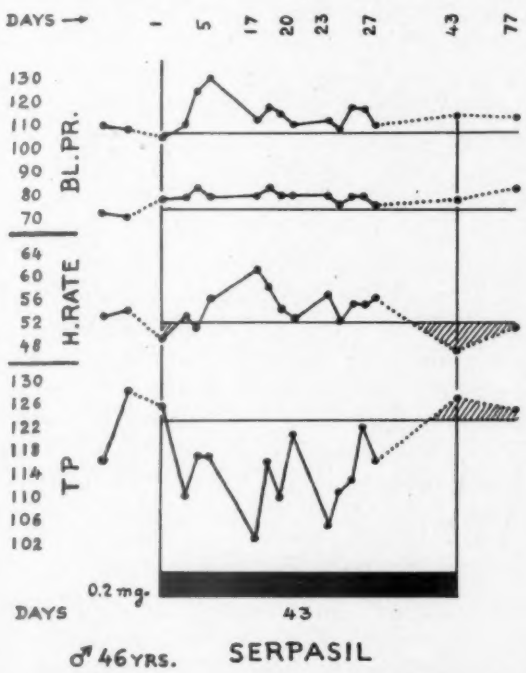

FIG. 4. Influence of reserpine on blood pressure, heart rate and isometric (tension) period of left ventricle. (Case 12.)

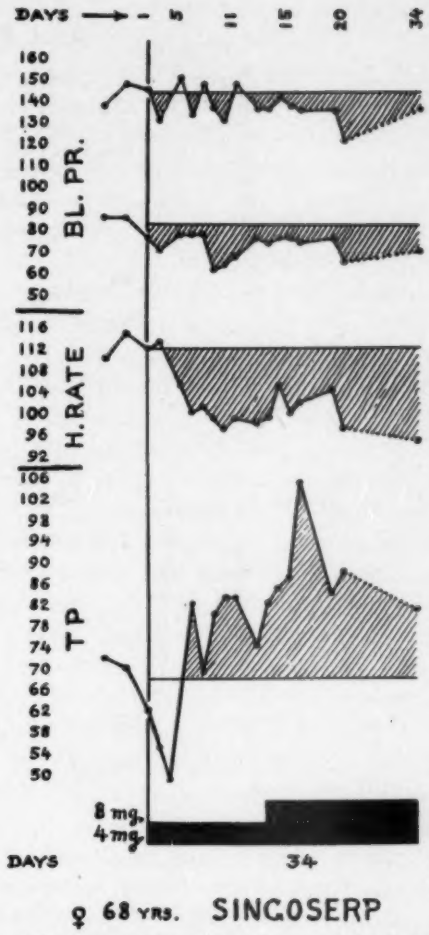

FIG. 5. Influence of syrosingopine on blood pressure, heart rate and isometric (tension) period of left ventricle. (Case 13.)

enings and shortenings within rather narrow limits. The ejection period was lengthened in six of the eight cases. In two instances (Cases 5 and 8), the intravenous injection was followed by dizziness, nausea, restlessness and drowsiness lasting several hours, and by an intense flushing of the skin.

Prolonged Medication with Small Doses: This produced the well-known slight tendency toward lowering of the systolic and diastolic blood pressure and a considerable reduction of the heart rate in Cases 9, 10, 11 and 13, whereas no such effects were noticeable in Case 12 (Figs. 1 to 5). A slight transient cardiac acceleration occurred during the first days of gradual "loading" with reserpine in Cases 9 and 11. After discontinuation of the drug the heart rate returned slowly toward its original level in Cases 9 and 10.

The isometric contraction or tension period showed a distinct although fluctuating increase in length in those subjects whose heart rates were also most significantly decreased (Cases

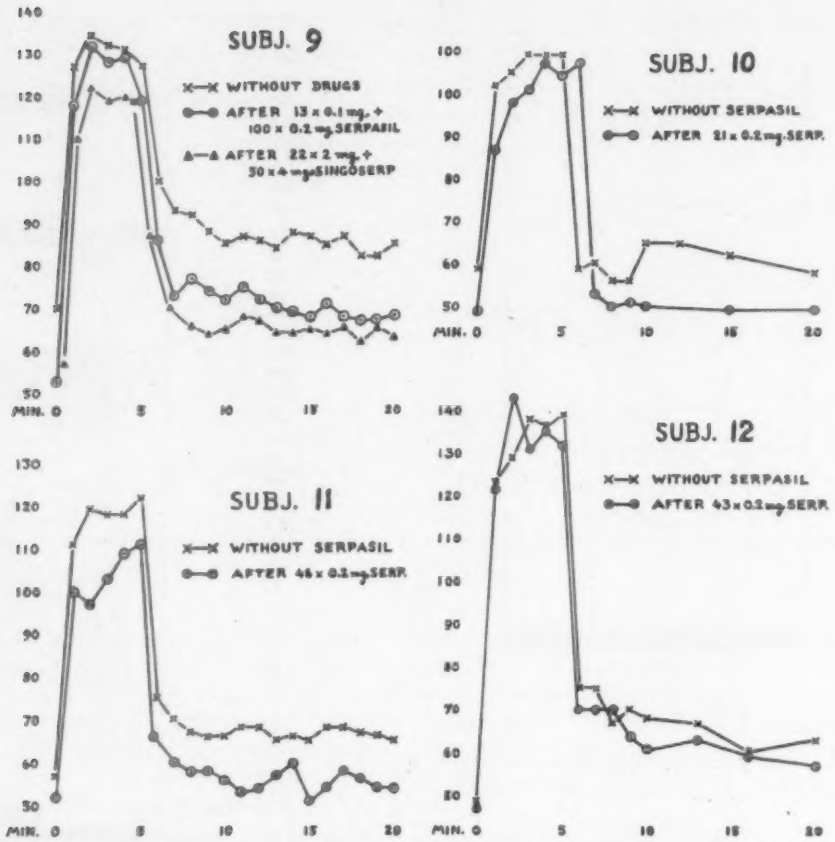
SUBJ. 9
X—X WITHOUT DRUGS
AFTER 13 x 0.1 mg. + 100 x 0.2 mg. SERPASIL
Δ—Δ AFTER 22 x 2 mg. + 30 x 4 mg. SINGOSERP
SUBJ. 10
X—X WITHOUT SERPASIL
AFTER 21 x 0.2 mg. SERP.
SUBJ. 11
X—X WITHOUT SERPASIL
AFTER 46 x 0.2 mg. SERP.
SUBJ. 12
X—X WITHOUT SERPASIL
AFTER 43 x 0.2 mg. SERP.
MIN. 0 5 10 15 20

FIG. 6. Influence of reserpine in Cases 9 through 12, and of syrosingopine in Case 9 on cardiac acceleration during, and cardiac deceleration after standard exercise on treadmill (walking five minutes at speed four miles per hour).

9, 10 and 13); it became, on the contrary, shortened (Cases 11 and 12). (The ejection period was measured in all instances but being largely a function of the heart rate[32] and, therefore, of only minor interest, was omitted from the graphs.)

Syrosingopine, administered in Cases 9 and 13 (Figs. 1 and 5), produced effects similar to reserpine (slight lowering of blood pressure, considerable reduction of heart rate and lengthening of tension period). Case 13 began with an unusually high heart rate and short tension period.

Exercise Tests: Individual differences in the response of the heart rate to exercise under the influence of rauwolfia drugs were manifested (Fig. 6) insofar as the exercise-induced accelerations were diminished in Cases 9, 10 and 11 (in Case 9 chiefly by syrosingopine, in the others by reserpine); whereas, the response of Case 12 who had also been refractory in other respects (Fig. 4) remained unchanged. Post-exercise cardiac deceleration was markedly intensified by reserpine and syrosingopine in Cases 9 to 11, but remained nearly unchanged in the generally refractory subject (Case 12).

Exercise Tests Without and With Atropinization: In Case 10 the cardiac acceleration by atropine alone was 35 beats per minute; during medication with reserpine (0.2 mg. daily for three weeks) it was augmented to 46 beats. The additional maximal exercise-induced acceleration under atropine alone was 40 beats; after pretreatment with reserpine it was 56 beats. The speed of post-exercise deceleration after atropinization was not significantly altered by reserpine.

In Case 12 the cardiac acceleration by atropine alone was nearly identical before and during medication with reserpine (0.2 mg. daily for six weeks); namely 35 vs. 39 beats. The same was true regarding the maximal exercise-induced acceleration after atropinization without and with reserpine (61 vs. 59 beats) and regarding the speed of deceleration.

COMMENTS

The mutual interferences between positive adrenergic catecholamine-liberating effects upon the heart of acute "loading" or "challenging" doses of rauwolfia drugs[6,27–29] and the anti-adrenergic catecholamine-depleting action of

the drugs[3,21–24] were manifested by the irregular and erratic chrono- and inotropic responses (the latter in agreement with the findings of Lasch[6]) occurring within hours after large intravenous dosages. In two subjects a slight initial cardiac acceleration and initial shortening of the isometric period preceded the typical cardiac slowing and prolongation of the tension period which accompanied the extended medication with smaller maintenance doses. Persistently paradoxical (positive adrenergic) responses were observed over longer periods in two instances. One subject (Case 11) showed a marked shortening of tension period, the other (Case 12) showed both cardiac acceleration and shortening of the tension period. This prolonged inverted reaction may be explained on the basis of the increased catecholamine sensitivity of catecholamine-depleted cardiovascular tissues.[2,3,22,30]

Under acutely injected large "loading" or "challenging" doses the chronotropic and inotropic effects, respectively, were often opposed to each other (Cases 1, 2, 4, 5, 8) whereas they appeared directionally coordinated during prolonged maintenance medication, with the exception of Case 11. The separate catecholamine supply from sympathetic nerve terminals in the atria (sinus area, responsible for heart rate) and ventricles (responsible for isometric period) probably accounts for the occasional dissociations of chronotropic and inotropic behavior. Doubling the prolonged dosage of both reserpine and syrosingopine did not seem to alter the bradycardic effect but in one instance (Case 13) it further prolonged the tension period.

The reduction of exercise-induced, catecholamine-mediated[35] tachycardia and the accentuated post-exercise deceleration under the influence of reserpine and syrosingopine (except in Case 12) resembled the effect of physical training on heart function[36] which intensifies antiadrenergic vagal and/or sympathoinhibitory mechanisms.[31] It is to be attributed to the partial catecholamine depletion of the heart muscle, and has also been observed by Schumann and Rehberg[14] and Weidmann and Klepzig.[37]

Catecholamine-hypersensitivity of the catecholamine-poor heart probably caused the seemingly paradoxical intensification of the atropine-induced cardiac acceleration, and of the tachycardia induced by atropine plus exercise after prolonged administration of reserpine in Case 10. One subject (Case 12) failed to display any influence of reserpine on the atropine–induced acceleration and the acceleration induced by atropine plus exercise.

The blood pressure responded to both acutely given large and prolonged small dosages of reserpine and syrosingopine with a consistent slight to moderate diminution in all subjects but one (Case 2).

It is worthy of note that this latter subject (Case 12) differed from the others on long term administration of medication by presenting an atypical response in all respects such as elevation of the systolic and diastolic blood pressure, cardiac acceleration and shortening of tension period. He was a forty-six year old, exceptionally tall sportsman (skier) with a resting heart rate of only 53 beats per minute and a long "athletic" tension period (117 thousands of a second). His high vagal and/or sympathoinhibitory tone was presumably acquired in part through his sports activities.[31,38,39] His living habits and cardiac functional features contrasted sharply with those of an unusually motionless subject (Case 13), a sixty-eight year old spinster (piano teacher) who had a resting heart rate of 113 beats per minute and an exceptionally short tension period (69 thousandths of a second), and who responded in a diametrically opposite fashion: lowering of the systolic and diastolic blood pressure, considerable reduction of the heart rate and marked prolongation of the tension period. A thirty-five year old physician (Case 10) also showed signs of a basic vagotonia and/or sympathetic inhibition. However, being physically quite inactive, he seemed to possess these peculiarities as a constitutional trait rather than by having acquired them through training. His responses to reserpine were quite typical.

Mechanisms Underlying Cardiovascular Reactions to Rauwolfia Drugs: Without speculating in detail regarding the underlying mechanisms responsible for the different patterns of cardiovascular reaction to reserpine in different test subjects, we believe that these observations suggest some dependence of the types of response to the rauwolfia drugs on the pre-existing basic neurovegetative neurohormonal status of the subject, whereby the degree of habitual physical activity seems to be involved. A direct proportion between the resting heart rate and the susceptibility to the cardioinhibitory action of the rauwolfia drugs has also been emphasized by other investigators.[6,7]

The literature concerning favorable clinical effects exerted by the rauwolfia drugs in a

variety of cardiac derangements and their essentially antiadrenergic mode of action (catecholamine depletion of the myocardium by "chemical sympathectomy"), agrees with the concept that an absolute or relative overactivity of the catecholamines norepinephrine and epinephrine in the heart muscle constitutes a hazard for myocardial functional and structural integrity.[26,40,41]

Therapeutic Application: Up to the present time, the main emphasis in the explanation of the beneficial results obtained by treatment with rauwolfia drugs has been placed on the negative chronotropic and vasodepressant effects of these drugs. Our present findings reveal, in addition, the existence of a marked negative inotropic antiadrenergic action, exerted by reserpine and syrosingopine on the human heart muscle (demonstrable on the left ventricle). This phenomenon is presumably due to inactivation of positively inotropically acting myocardial norepinephrine, whose efficiency-impairing, oxygen-wasting, potentially hypoxiating (in the subendocardial layers[41]) and ultimately necrotizing[40,42] properties are being increasingly appreciated.[43]

Subjects with a high sympathetic tone (adrenergic preponderance[31]) seem to respond particularly readily to the negative chronotropic and inotropic actions of the rauwolfia drugs, and a more extensive therapeutic testing of these drugs, especially of those without cerebral side effects (e.g. syrosingopine) in combination with customary basic medications, appears indicated. In consideration of the transient, paradoxically adrenergic effects of large early "loading" doses, it would seem advisable to begin the therapeutic application of rauwolfia drugs in cardiac patients with small amounts (e.g. 0.1 mg. reserpine; 2 mg. syrosingopine) and to increase them gradually to a maintenance level rather than proceeding in the opposite direction.

Summary

1. The effects of rauwolfia drugs on cardiac function are complex. Prolonged administration of small doses of reserpine and syrosingopine lowered the blood pressure and reduced the heart rate and, in three subjects, exerted a negative inotropic effect on the normal heart (prolongation of the isometric contraction period of the left ventricle). This effect is presumably due to depletion of myocardial norepinephrine. An opposite reaction of the isometric period which occurred in two subjects may be attributable to the co-existing catecholamine hypersensitivity of catecholamine-depleted cardiovascular tissues.

2. Exercise-induced tachycardia was generally diminished and post-exercise cardiac deceleration accentuated by administration of reserpine.

3. The degree of the negative chronotropic and, to some extent, also of the negative inotropic effect of the rauwolfia drugs seems to be directly proportionate to the pre-existing basic sympathetic tone.

4. Large, acutely injected "loading doses" of reserpine lowered the blood pressure within a few hours but produced inconsistent and erratic chronotropic and inotropic reactions of the heart (probably dependent on the prevalence of either liberation or early depletion of cardiac catecholamines, respectively).

5. The antiadrenergic negative chronotropic and inotropic properties of the rauwolfia drugs seem to qualify them as useful agents for selected subjects displaying a potentially detrimental cardiac adrenergic preponderance, and for supplementary medication in such catecholamine-induced conditions as angina pectoris, certain types of congestive heart failure and tachycardias.

Acknowledgment

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Experimental Study

Angina Pectoris

IV. Clinical and Experimental Difference Between Ischemia with S-T Elevation and Ischemia with S-T Depression*

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ACCORDING TO CLASSIC cardiographic theory S-T segment elevation is produced predominantly by acute coronary occlusion. This was first observed in man by Pardee[1] and by Wolferth and Wood.[2,3] Subsequently, Wood, Wolferth and Livezey[4] reproduced in animal experiments similar elevation of the S-T segment following occlusion of a large coronary artery. It has been demonstrated[5] that S-T segment elevation may also occur during attacks of the variant form of angina pectoris.

S-T segment depression recorded at the epicardium is explained, according to classic electrocardiographic theory, by reciprocity from an injury current in the underlying subendocardium.[6] By contrast, electrocardiographic patterns clinically observed in patients with classic angina and in some cases of mild myocardial infarction[7] suggest a theory of primary S-T segment depression. Experimental evidence in favor of this theory has been presented.[8] Experimentally, primary S-T segment depression has been produced by hemorrhagic hypotension[8] and by injection of solutions of varying ionic concentration into the extracellular medium.[9]

Fundamental clinical, physiologic, chemical and metabolic differences between ischemic conditions with S-T elevation and those with S-T depression have been demonstrated.[9] In the course of these studies,[8] differences in color between these two types of ischemia were also noted; ischemic myocardium with S-T elevation was usually cyanotic and ischemic myocardium with S-T depression was a normal red color.

Experiments were performed in dogs in order to study more precisely the differences between S-T segment elevation and S-T segment depression and their relationship to varying degrees of myocardial ischemia. Such differences need further exploration because some cases of myocardial infarction show S-T segment depression although most show S-T segment elevation. This is also seen in angina pectoris; some cases show S-T segment elevation although most show S-T segment depression. Evidence supporting the theory of *primary* S-T depression is presented.

METHOD

Forty-two mongrel dogs, weighing between 13 and 25 kg., were used in these experiments; some of the dogs were used in more than one experimental group. They were anesthetized with pentobarbital sodium administered intravenously in doses averaging 25 mg. per kg. of body weight. The chest was opened and a large branch of the anterior descending coronary artery was exposed. Tiny electrodes measuring 0.1 mm. by 2 mm. were attached to the pericardium at selected points over the area supplied by this artery, and control electrocardiograms were recorded.

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TABLE I
S-T Changes After Ligation of a Large Coronary Artery (Experiment 1)

Portion of Ischemic Area	Amplitude of S-T Elevation (mv.)				
	Before Ligation	After Ligation			
		1–2 min.	3 min.	5 min.	10 min.
Central	1.33 ± 0.34	7.63 ± 0.85*	8.42 ± 1.13*	9.88 ± 1.02*	11.33 ± 1.71*
Intermediate	2.16 ± 0.38	5.0 ± 0.37*	...	6.67 ± 0.49*	7.75 ± 0.11*
Peripheral	0.5 ± 0.16	0.8 ± 0.53	1.33 ± 0.62	2.11 ± 0.57†	2.75 ± 0.28*

Note: Values are mean ± S. E. At the periphery there was some S-T elevation during the first three minutes after ligation even though the difference was not statistically significant ($P < 0.05$).
* Highly significant difference compared with control value ($P < 0.003$).
† Significant difference compared with control value ($P < 0.05$).

RESULTS

EXPERIMENT 1: S-T RESPONSE TO OCCLUSION OF A CORONARY ARTERY

S-T Elevation: Forty-seven separate experiments were performed in twenty-three dogs. A large branch of the anterior descending coronary artery was ligated, producing a distal area of ischemia. About a half minute later, S-T segment elevation began to appear from the epicardial leads over the *central part* of the ischemic area, then in succession from the *intermediate zone* and from the *periphery* (Table 1). The amplitude of S-T segment elevation increased over the next few minutes, usually becoming relatively stabilized about five min-

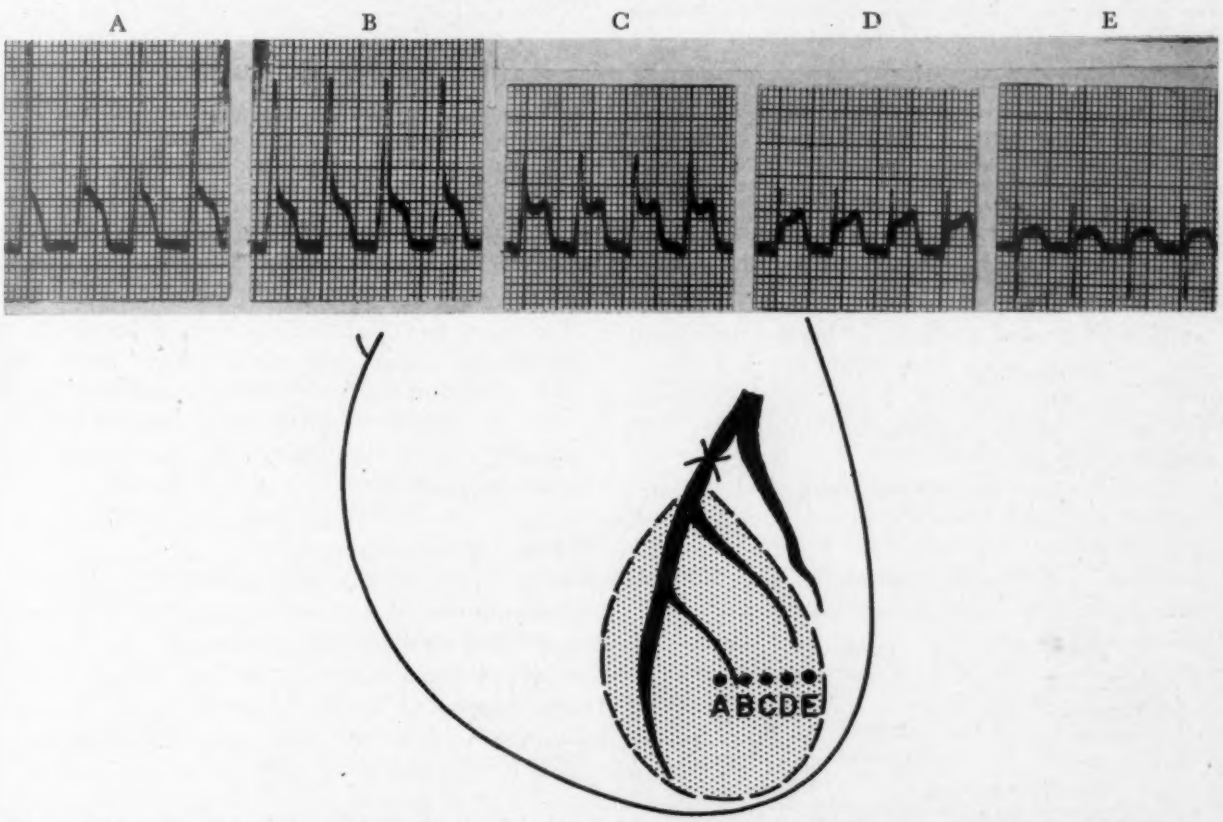


FIG. 1. S-T segment changes following ligation of a large coronary artery. Tracings were made by means of an exploring electrode at points A through E which are progressively farther from the center of the ischemic area. S-T elevation occurred first and was greatest from the central part, developing later and to a lesser degree toward the periphery. Note also the giant R wave and receding S wave in the regions of greatest ischemia.

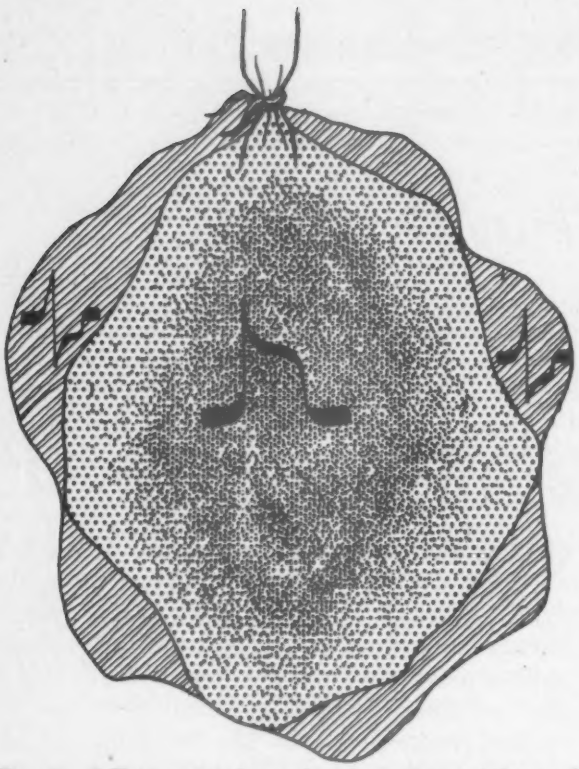


FIG. 2. S-T segment depression from the periphery of an ischemic area. About fifteen minutes after ligation of a large coronary artery S-T segment depression, varying in amplitude up to 3 mv., was recorded from the irregular, narrow, reddish-blue sections which had appeared along the periphery of the ischemic area. Cyanosis was more marked in the center of the ischemic area, less pronounced toward the periphery.

utes after ligation of the artery. By means of an exploring electrode, S-T segment elevation was found to be most pronounced from the central part of the ischemic area. This increased amplitude proved statistically highly significant one to two minutes after ligation. S-T elevation was less marked from the periphery, becoming highly significant only after ten minutes (Fig. 1).

In nine dogs a large monophasic curve appeared from the central part of the ischemic area. In this area in the remaining fourteen animals no monophasic curve appeared but there was marked S-T elevation.

S-T Depression: About fifteen to twenty minutes after ligation of the artery, slight S-T segment depression was noted in most tracings from the periphery of the ischemic area. (One exception was noted in which S-T depression from the periphery appeared almost immediately after ligation of the coronary artery, simultaneous with S-T elevation over the central part of the ischemic area.) The amplitude of the S-T depression increased progressively and after twenty minutes or more reached a level of as much as 3 mv. At all times the peripheral area in which an S-T segment depression could be recorded was narrow and of irregular shape.

A large cyanotic area developed in all animals immediately after ligation of the coronary artery. Cyanosis was more marked in the center of the ischemic area and less pronounced toward the periphery. Somewhat later, the color generally changed to reddish-blue in irregular narrow patches along the margin of the cyanotic area. Recordings from these reddish-blue patches most often revealed S-T depression (Fig. 2). With the passage of time the central cyanotic area diminished in size and the reddish-blue patches appeared to shift inward. At all times the myocardium beyond the ischemic area was of normal red color.

S-T depression was also recorded from an area of the posterior wall of the heart opposite to the ischemic area in the anterior wall (Fig. 3). This S-T depression, long recognized as reciprocal, appeared *simultaneously* with the S-T elevation from the anterior ischemic area; S-T depression recorded from around the periphery of the ischemic area appeared *later* and *independently*.

TABLE II

S-T Response During Ligation and After Release of Tie on Coronary Artery (Experiment 2)

Portion of Ischemic Area	Amplitude of S-T Deviation (mv.)			
	Before Ligation	During Ligation		After Release
		5 min.	30 min.	
Central	1.50 ± 0.40	7.75 ± 0.69*	6.67 ± 0.88*	−1.12 ± 0.055*

Note: Values are mean ±S.E.

* Highly significant difference compared with control value ($P < 0.003$).

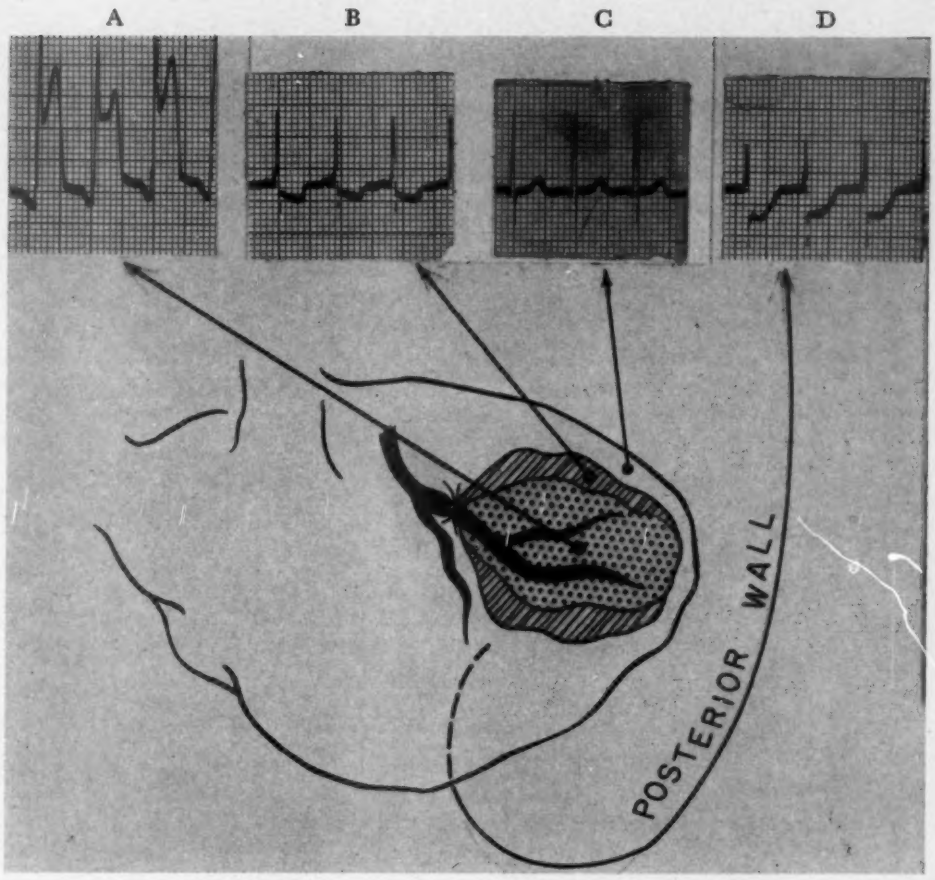


FIG. 3. S-T segment response to ligation of a large coronary artery. A, marked S-T elevation from the central part of the ischemic area located in the anterior wall appeared very shortly after ligation of a large branch of the anterior descending coronary artery. B, S-T segment depression appeared from irregular, narrow sections along the periphery of the ischemic area about fifteen minutes after ligation of the artery. C, the S-T segment recorded beyond the periphery of the ischemic area (between points B and D) was isoelectric. D, reciprocal S-T segment depression appeared over the posterior wall of the heart opposite to the ischemic area simultaneously with the appearance of S-T elevation from the ischemic area.

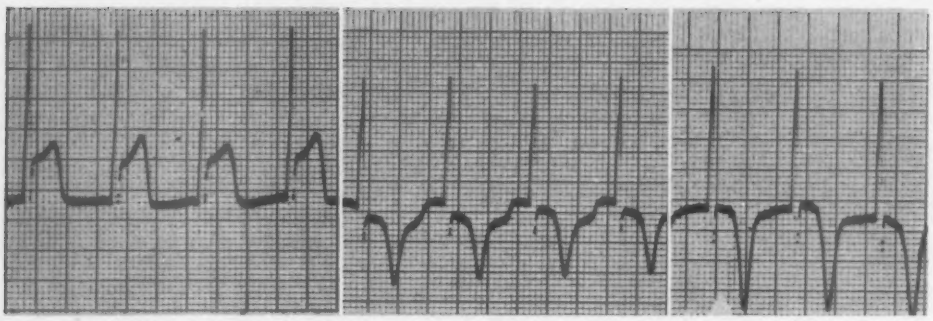
EXPERIMENT 2: S-T RESPONSE TO RELEASING TIE ON A CORONARY ARTERY

In nine dogs, sixteen separate experiments were performed in which a large branch of the anterior descending coronary artery was ligated, resulting in a large cyanotic area of ischemia. S-T segment elevation appeared over the ischemic area, becoming relatively stabilized in the central part about five minutes after ligation of the artery. At this time slight S-T segment elevation was recorded from the periphery of the ischemic area. The tie on the coronary artery was released after thirty minutes (Table II).

After re-establishing the blood flow the degree of ischemia began to diminish. Immediately, the cyanotic color began to fade and change to bright red, indicating reactive hyperemia. Transient S-T depression appeared where S-T elevation had previously been recorded, first from the periphery (about two minutes after release of the tie) and then from the central part of the ischemic area (about three minutes after release of the tie). Subsequently, the S-T segment stabilized on the isoelectric line (Fig. 4). The transient S-T depression was statistically highly significant for the group as a whole; however, S-T segment elevation persisted in two dogs, although at a somewhat diminished level following release of the tie.

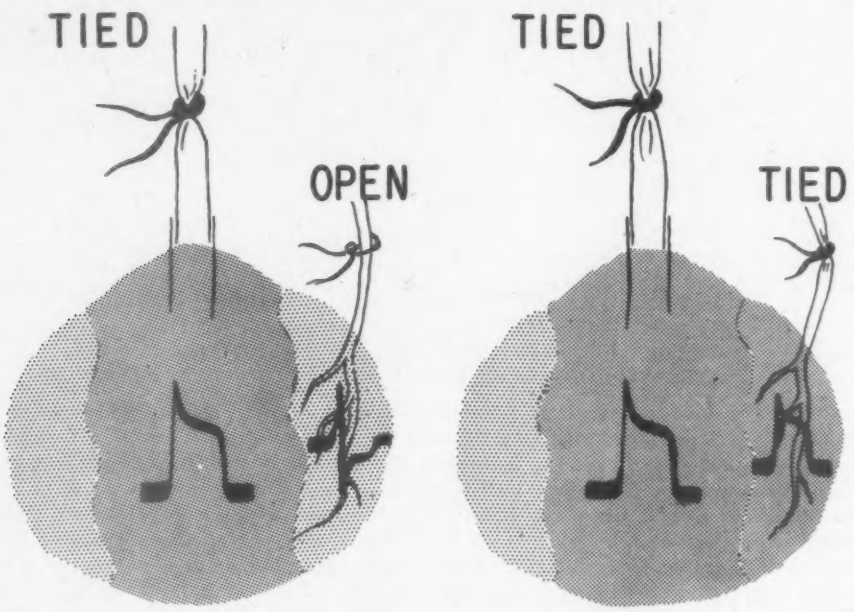
EXPERIMENT 3: S-T RESPONSE TO TYING AN ADJACENT CORONARY ARTERY

In ten dogs (ten individual experiments), a large branch of the anterior descending coronary artery was ligated as in experiments



A B C

FIG. 4. S-T segment response to releasing the tie on a large coronary artery. Tracings from a fixed electrode over the central part of the ischemic area. A, five minutes after ligation of the artery—S-T segment elevation. B, three minutes after release of the tie—transient S-T depression. C, about five minutes after release of the tie—S-T segment stabilized on the isoelectric line.



A B

FIG. 5. S-T segment response to tying an adjacent coronary artery. A, twenty minutes after ligation of a large coronary artery: S-T segment elevation over the central part of the ischemic area; S-T segment depression from the periphery. B, after ligation of a second coronary artery supplying the adjacent myocardium: S-T depression from the periphery of the original ischemic area is replaced by S-T elevation.

1 and 2. Irregular narrow patches of reddish-blue myocardium appeared again along the periphery of the central cyanotic area and S-T segment depression was usually recorded from the periphery (Fig. 5A). Twenty minutes after ligation of the large branch of the artery a second, smaller branch of the anterior descending coronary artery supplying the myocardium at the periphery of the ischemic area was ligated (Fig. 5B). The S-T depression from the periphery of the original ischemic area near this second ligation was replaced by S-T elevation and the reddish-blue myocardium became deeply cyanotic.

EXPERIMENT 4: S-T RESPONSE TO CHANGES IN BLOOD SUPPLY TO PERIPHERY OF AN ISCHEMIC AREA

Three dogs were used in this experiment; nine separate experiments were conducted. Two artificial coronary artery circuits were utilized to provide a method for studying the S-T segment response to varying degrees of reduced blood supply.

Circuit A: The *left carotid artery* and a large branch of the anterior descending coronary artery were ligated and cut. The proximal segment of the carotid artery was connected by means of a catheter to the distal segment of the

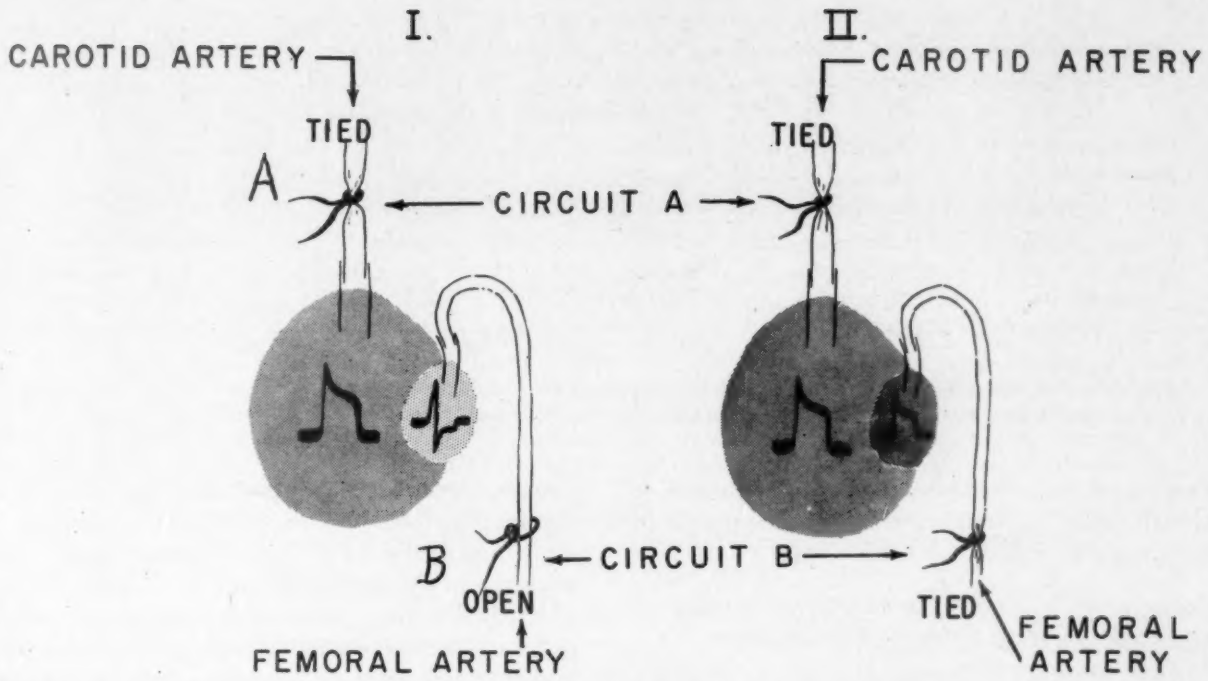


FIG. 6. S-T segment response to changes in the blood supply to the periphery of an ischemic area. Circuit A connected the left carotid artery to a large branch of the anterior descending coronary artery. Circuit B connected the left femoral artery to a small branch of the anterior descending coronary artery supplying the myocardium at the periphery of the central area. I, closure of circuit A resulted in a large area of ischemia with S-T elevation. After fifteen to twenty minutes S-T depression appeared from a narrow section at the periphery of the ischemic area. II, subsequent closure of circuit B increased the severity of ischemia at the periphery with S-T depression being replaced by S-T elevation. Numerous variations of this experiment were performed with similar results.

coronary artery, thus controlling the blood flow to the area supplied by this artery designated as "area A" (Fig. 6).

Circuit B: The *left femoral artery* and a small branch of the anterior descending coronary artery supplying the myocardium at the periphery of area A were ligated and cut. The proximal segment of the femoral artery was connected by means of a catheter to the distal segment of this small branch artery, thus controlling the blood flow to this small area of the myocardium (designated as "area B").

Each circuit could be controlled independently by opening and closing clamps placed over the catheters. (1) Circuit A was closed, resulting in a large area of ischemia with S-T elevation. Approximately fifteen to twenty minutes later, S-T segment depression usually appeared from the periphery of this large ischemic area (Fig. 6I). Twenty-five minutes after closing circuit A, circuit B was also closed in order to increase ischemia in the peripheral area (Fig. 6II). About a half minute after closing circuit B, S-T segment depression from area B was usually replaced by S-T segment elevation. At the same time the color of the myocardium in this area changed from reddish-blue to deeply cyanotic. (2) Circuit B was then reopened to increase the blood supply to area B. In approximately two to three minutes S-T elevation disappeared and S-T depression was again recorded from this area. At the same time the irregular reddish-blue color reappeared. (3) The experiment was then modified by reversing the sequence of the procedure as follows: circuit B was closed first, resulting in ischemia in area B with epicardial S-T elevation. Irregular reddish-blue patches appeared at the margin of this small ischemic area. Fifteen to twenty minutes after closure of circuit B, S-T segment depression began to appear from the margin of area B. Twenty-five minutes after closure of circuit B, circuit A was also closed. About a half minute after closing circuit A, S-T depression from the zone where areas A and B adjoined was replaced by S-T elevation. The color of the myocardium in this zone changed from reddish-blue to cyanotic. Subsequently, circuit A was reopened while circuit B remained closed. In two to three minutes S-T segment

TABLE III
S-T Response to Hemorrhagic Hypotension and Transfusion after Ligation of Coronary Artery (Experiment 5)

Portion of Ischemic Area	Amplitude of S-T Deviation (mv.)			
	Before Ligation	After Ligation (5 min.)	After Hemorrhagic Hypotension	Transfusion
Central	0.91 ± 0.29	9.29 ± 1.15*	12.0 ± 1.35*	6.67 ± 1.08*
Intermediate	1.06 ± 0.24	2.50 ± 0.57†	2.8 ± 0.97	−0.7 ± 0.65†

Note: Values are mean ± S.E.
* Highly significant difference compared with control value ($P < 0.003$).
† Significant difference compared with control value ($P < 0.05$).

depression was recorded from the margin of area B, often accompanied by reappearance of the irregular reddish-blue patches.

EXPERIMENT 5: S-T RESPONSE IN AN ISCHEMIC AREA TO (A) HEMORRHAGIC HYPOTENSION AND (B) TRANSFUSION

In fourteen dogs, twenty-five separate experiments were performed in which a large branch of the anterior descending coronary artery was ligated. The central part of the ischemic area thus produced showed S-T segment elevation which usually became relatively stabilized about five minutes after ligation of the artery.

Hemorrhagic hypotension (experiment 5A): Hemorrhagic hypotension was produced by reducing the mean pressure in the femoral artery to approximately 40 mm. Hg. This further increased the S-T elevation from the central part of the ischemic area (Fig. 7) (Table III).

S-T segment elevation from the intermediate zone increased slightly. The zone immediately outside the ischemic area, in which the S-T segment had been isoelectric prior to hypotension, now also showed slight S-T elevation, and the area of cyanosis appeared enlarged. Electrocardiographic exploration beyond the large ischemic area revealed "islands" of S-T depression scattered over all aspects of both ventricles.

Transfusion and return to normal blood pressure (experiment 5B): Following a period of hypotension lasting ten to fifteen minutes, the dogs were transfused with the blood which had been removed, approximately restoring the mean blood pressure to the pre-bleeding level.

Elevation of the S-T segment decreased from the central part of the ischemic area (Fig. 8) (Table III). S-T segment depression was recorded from the periphery of the ischemic area. Immediately after transfusion, the size of the cyanotic area seemed to decrease and reddish-blue patches gradually appeared at the periphery. The scattered "islands" of S-T segment depression which had been recorded over all aspects of both ventricles during hypotension disappeared following transfusion.

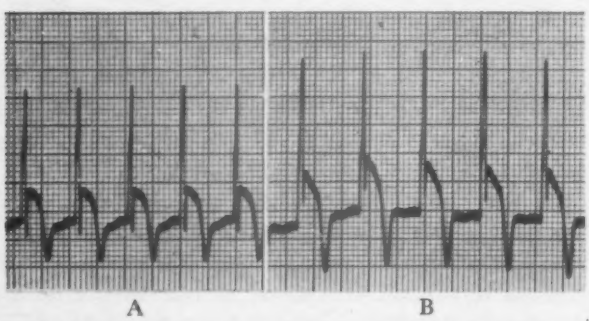


FIG. 7. S-T segment response to hemorrhagic hypotension in an ischemic area. A, after ligation of a large branch of the coronary artery: S-T segment elevation (5 mv.) from the central part of the ischemic area. B, five minutes after lowering the mean blood pressure to 40 mm. Hg: Further elevation of the S-T segment (8 mv.). Note also the increase in the R wave and the decrease in the S wave.

FIG. 8. S-T segment response to transfusion following hemorrhagic hypotension in an ischemic area. A, after ligation of a large branch of the coronary artery and subsequent lowering of the mean blood pressure to 40 mm. Hg: Marked S-T elevation (8 mv.). B, after transfusion and return to normal pressure: Decrease in S-T segment elevation (5 mv.).

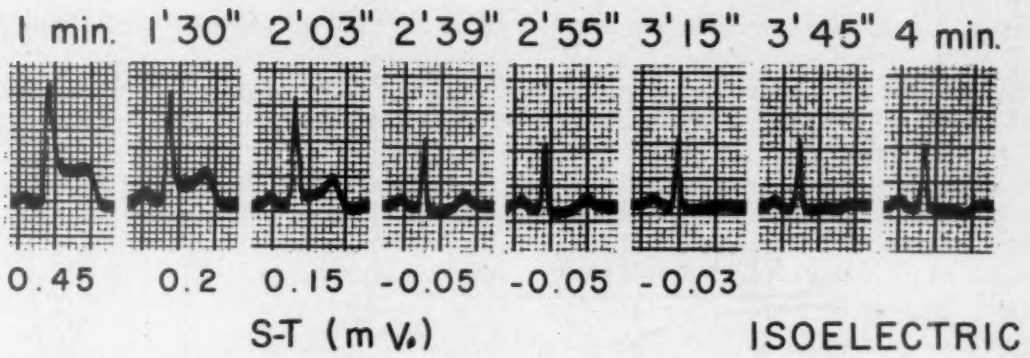


FIG. 9. S-T segment changes during and after an attack of the variant form of angina pectoris. Selected complexes of a continuous tracing from an umbilical lead facing the ischemic area on the diaphragmatic surface of the heart. One minute after the onset of the attack the pain was severe and marked S-T elevation was recorded. As the pain began to diminish (at about one and a half minutes) the S-T elevation started to decrease. The pain ceased at about two minutes. Subsequently, transient S-T depression appeared. Finally, the S-T segment stabilized on the isoelectric line. (From: PRINZMETAL, M., EKMEKCI, A., TOYOSHIMA, H. and KWOCZYNSKI, J. K. *Am. J. Cardiol.*, 3: 276, 1959.[9])

COMMENTS

The striking finding in all five experiments is that *S-T segment elevation is associated with more severe ischemia than S-T segment depression.*

In experiment 1, confirming the earlier observation by Rakita et al.,[10] it was demonstrated that after ligation of a coronary artery elevation of the S-T segment is greatest from the central part of the ischemic area and less pronounced from the intermediate zone or at the periphery. Ischemia is, in all likelihood, most severe in the central part of the area supplied by the ligated coronary artery. It follows, therefore, that greater S-T elevation coincides with a higher degree of ischemia.

S-T depression appearing from the reddish-blue patches at the periphery of the ischemic area had already been observed by Wolferth et al.[6] and by Hellerstein and Katz.[11] Ischemia is presumed to be more severe in the central part than at the periphery; therefore, it would appear that S-T elevation is associated with a higher degree of ischemia than is S-T depression.

This conclusion is strengthened by the observations in experiment 2. When the tie on the coronary artery was released, ischemia progressively diminished and S-T segment elevation was usually replaced by transient S-T depression. Changes similar to those experimentally produced by releasing the tie and restoring the blood supply have been observed in some cases of the variant form of angina.[5,9] During severe pain, S-T segment elevation is recorded from the standard and precordial leads. This is followed by transient S-T depression as the pain subsides (Fig. 9).

A typical case is that of a forty-nine year old man with the variant form of angina who experienced frequent episodes of anginal pain while at rest. As previously reported,[9] an electrocardiogram was recorded during and after an episode of severe pain. From an umbilical lead facing the ischemic diaphragmatic surface of the heart, marked elevation of the S-T segment was noted as long as the severe pain lasted (Fig. 9). When the pain began to diminish (about a minute and a half after onset) S-T elevation started to decrease. The pain ceased at two minutes, and half a minute later transient S-T depression appeared until finally the S-T segment stabilized on the isoelectric line.

These electrocardiographic changes occurring during an attack of the variant form of angina are identical with the changes noted in experiments with animals upon release of the tie on a large coronary artery. This lends support to the hypothesis that *hypertonicity* in a large coronary artery already partly narrowed may produce clinically a temporary occlusion similar to that observed after experimental ligation of an artery.[5]

The same relationship between degree of ischemia and configuration of the S-T segment was demonstrated in another manner in experiment 3. As ischemia at the periphery of the ischemic area was increased by ligating an adjoining coronary artery, the reddish-blue myocardium changed to a deeply cyanotic

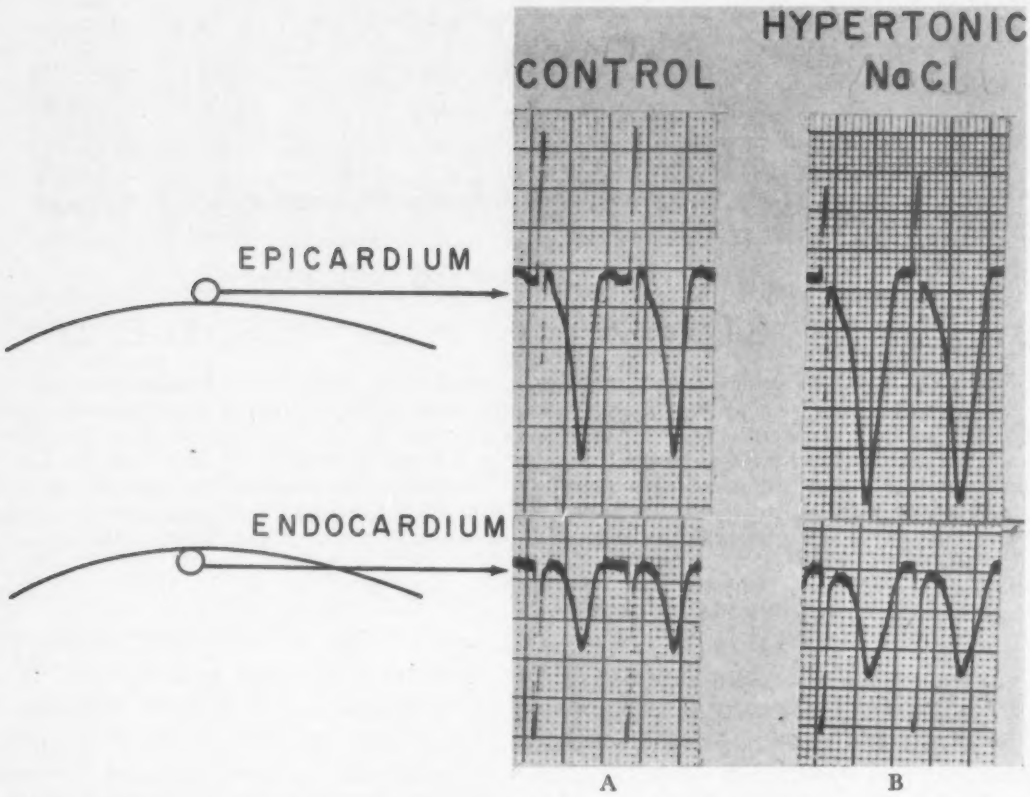


FIG. 10. Simultaneous S-T depression from epicardial and underlying endocardial leads after injection of high concentration sodium chloride solution (171 mEq./L. NaCl). Simultaneous records obtained from the epicardium and from the endocardium. A, controls. B, about three seconds after injection into the coronary artery circuit: S-T depression recorded from both epicardium and endocardium. (Note: There is less S-T segment change from the endocardial than from the epicardial lead.)

color and S-T depression was replaced by S-T elevation. The converse is also true as was demonstrated in experiment 4 when one or the other of the two circuits was opened. With increased blood supply the color of the myocardium at the borderline between the two areas usually changed from cyanotic to reddish-blue and at the same time S-T elevation was replaced by S-T depression.

Further reduction in the blood supply to the ischemic area as produced by hemorrhagic hypotension in experiment 5A resulted in an increase of S-T segment elevation from the entire ischemic area plus the appearance of "islands" of S-T depression over all aspects of both ventricles. It is well known that cardiovascular shock complicating acute coronary occlusion is responsible for a tremendous increase in mortality. According to Grishman and Master,[12] cardiovascular shock leads to further decrease in coronary flow and thereby a further reduction in the blood supply to the ischemic area.

The "islands" of S-T depression scattered over the epicardial aspect of both ventricles, as observed in experiment 5A, are comparable to clinical findings in classic angina pectoris which were reported previously.[8] This experiment demonstrates what might occur in patients having classic angina with "islands" of S-T depression combined with variant angina with a large area of S-T elevation.

The changes produced by hemorrhagic hypotension were reversed after transfusion and return of systemic blood pressure to the prebleeding level (experiment 5B). This demonstrates that raising the blood pressure reduces the severity of ischemia and its manifestations.

PRIMARY S-T DEPRESSION

In patients with classic angina pectoris S-T depression recorded from precordial leads has been attributed by Wolferth et al.[6] and by Myers et al.[13,14] to the reciprocal effect of subendocardial injury currents. In the meantime, however, a number of clinical and experi-

mental observations have been made which force us to recognize *primary* S-T depression, i.e., S-T depression indicative of ischemia from the region of the exploring electrode and not produced by the reciprocal effect of subendocardial ischemia.

In a large number of experiments[8,10] it has been demonstrated that hemorrhagic hypotension may produce marked S-T depression from direct epicardial leads without significant S-T elevation from simultaneously recorded subendocardial and cavity leads. These findings were confirmed by Toyoshima et al.[15] through the use of multiple intramural electrodes. These experiments produced no marked S-T elevation from subendocardial or cavity leads; therefore, the epicardial S-T depression cannot be explained on the basis of the reciprocal effect of a subendocardial injury current. Massumi et al.[16] demonstrated that the converse is also true: injury to the outer layers of the myocardium resulting in marked epicardial S-T segment elevation failed to produce any significant displacement of the S-T segment from the subendocardial or cavity leads.

Clinical observations point in the same direction. In subendocardial fibroelastosis severe lesions of the endocardium and subendocardium may exist without producing S-T segment depression.[8] In some instances of mild myocardial infarction in which it must be assumed that the subendocardial infarct extends to some degree to the outer layers, S-T depression rather than S-T elevation occurs.[7] In chronic pericarditis, even though only a thin shell of subepicardial tissue is diseased, S-T depression may be recorded.[17] In idiopathic hypertrophy of the heart there may be marked S-T segment depression without disproportionate involvement of endocardium and subendocardium.[8]

Considered purely on a mathematical basis it is very doubtful whether epicardial S-T depression is always reciprocal to a subendocardial injury current. This may be illustrated by a hypothetical example.[9] A subendocardial lesion measuring 1 cm. in diameter is assumed to lie in a ventricular wall measuring 1 cm. in thickness. One electrode is placed in the cavity directly over the center of the subendocardial area of injury and a second electrode is placed in a corresponding position at the epicardium directly opposite to the cavity electrode. Under these circumstances, the magnitude of the reciprocal S-T depression at the epicardial surface would be only about $^1/_{10}$ that of the S-T elevation recorded in the cavity. This relationship can be expressed mathematically by the "solid angle value"* which at the endocardial surface is approximately 2π, while at the epicardial surface it is $0.21\ \pi$. Thus, if a comparatively small reciprocal S-T depression of up to 0.3 mv. were recorded at the epicardial surface, it would require that a very large S-T elevation of up to 3 mv. be recorded in the cavity. Even if the injured area is assumed to be of a different thickness and the electrodes placed in a less precise position, a large disparity between the reciprocal epicardial S-T depression and the cavity S-T elevation would nonetheless be expected.

Cellular Responses in S-T Elevation and S-T Depression: It might be reasoned at this point that epicardial S-T depression may occur in response to a change in the subepicardium. From this it would follow that myocardial cells are capable of two different types of response; one producing S-T elevation, the other S-T depression. Such an assumption is not at variance with fundamental electrocardiographic theory and is entirely compatible with the principle of reciprocity. Primary S-T depression must be associated with reciprocal S-T elevation in the same way that primary S-T elevation is associated with reciprocal S-T depression. In many cases of primary S-T depression the reciprocal S-T elevation may be found in aVR and aVL leads, depending on circumstances.

Two different types of cellular response resulting in S-T segment deviation have been recently demonstrated.[9] These changes occurred with ischemic as well as nonischemic conditions and were brought on by chemical factors. When a *hypotonic* sodium solution was rapidly injected into a coronary artery, local transient S-T segment *elevation* resulted. Injection of a *hypertonic* sodium solution produced transient S-T segment *depression*. Potassium solutions in different concentrations also produced opposite S-T segment responses. Injection of a *high concentration* potassium solution resulted in transient S-T *elevation* while injection of a *low concentration* potassium solution produced S-T *depression*. These perfusion experiments reveal that either S-T elevation or S-T depression may occur over the same area of the myocardium, the direction of the S-T deviation

* "Solid angle value" is a geometric value used to express the three dimensional relationship of a point (P) to a portion of a spherical surface intersected by a solid cone from the point.

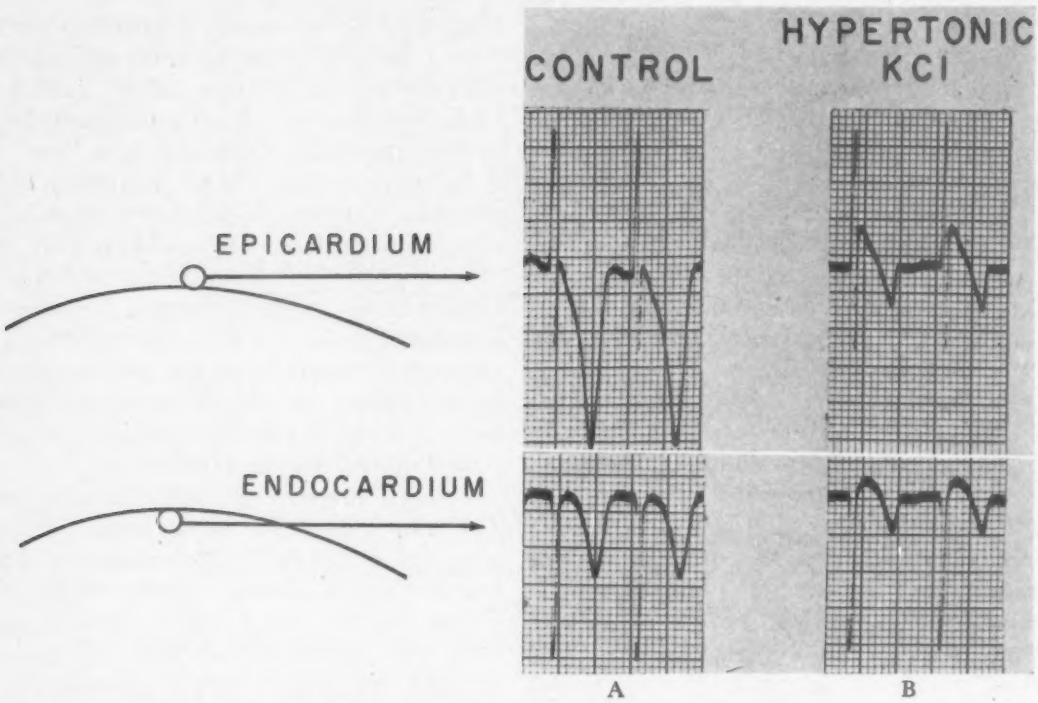


FIG. 11. Simultaneous S-T elevation from epicardial and underlying endocardial leads after injection of high concentration potassium chloride solution (6 mEq./L. K in 142 mEq./L. NaCl). Simultaneous records obtained from the epicardium and from the endocardium. A, controls. B, about three seconds after injection into the coronary artery circuit: S-T elevation recorded at both epicardium and endocardium. (Note: There is less S-T segment change from the endocardial than from the epicardial lead.)

depending on the nature and concentration of the solution injected.

It seems clear that however many solutions are used, as long as they are injected through the same cannulas they will affect the same cells; it is hardly plausible that they would migrate to various sites, causing different cells to react. We can account for the occurrence of both S-T elevation and S-T depression over the same area of the myocardium in the perfusion experiments only if it is assumed that the *same cell* is capable of giving rise to *primary S-T elevation* and also to *primary S-T depression.*

According to classic theory the S-T segment response to myocardial injury is elevation only. By supposing that the cell undergoes somewhat similar changes with injection of solutions as with injury, the S-T elevation encountered in the perfusion experiments can be readily explained. But to what can we attribute the S-T depression after the injection of high concentration sodium or low concentration potassium solutions? Since there seems no other way to resolve the problem presented by these and similar findings it becomes necessary to recognize the possibility of a primary S-T depression.

This hypothesis is supported by a number of observations. Unpublished experiments have shown that injection of a high concentration sodium chloride solution into a coronary artery circuit produced marked S-T depression *simultaneously* from epicardial and from underlying endocardial leads (Fig. 10). Injection of a high concentration potassium chloride solution into the coronary artery circuit produced S-T elevation *simultaneously* from the same epicardial and underlying endocardial leads (Fig. 11). By injecting a dye into this coronary artery circuit, it was subsequently demonstrated that both the epicardial and the underlying endocardial electrodes were in contact with myocardium supplied by the same coronary artery.

Furthermore, when the tie on a large coronary artery was released thirty minutes after ligation (experiment 2), S-T segment elevation from the central part of the ischemic area decreased and was in almost all instances replaced by transient S-T depression. As this S-T depression occurred *after the disappearance* of the S-T elevation it could not be reciprocal to S-T elevation and in our opinion also represents primary S-T depression.

Primary vs. Reciprocal S-T Depression: It would also be difficult to explain the S-T depression recorded from the periphery of the ischemic area (experiment 1) exclusively on the basis of reciprocity to S-T elevation from the central part of the ischemic area. S-T depression from the periphery of the ischemic area measured up to 3 mv. in depth and appeared from points where slight or moderate S-T elevation had been previously noted. The potential of exploratory electrodes placed over these marginal patches would be too small to account for the magnitude of S-T depression recorded.

Other factors argue against an explanation of primary S-T depression on the basis of reciprocity. When first observed about fifteen minutes after ligation of the coronary artery, S-T depression from the periphery was usually shallow but subsequently tended to increase in depth. At the same time the size of the ischemic area tended to *decrease* (experiment 1). These two changes could not occur simultaneously if the S-T depression were, indeed, reciprocal. In fact, the *reverse* would be found; that is, due to the curvature of the heart the solid angle values at leads placed at the periphery would decrease as the ischemic area contracted and S-T depression would then also decrease. Therefore, an *increasing* depth of S-T depression from the periphery at this time invalidates an explanation in terms of reciprocity.

The time factor, too, bolsters the case for primary S-T depression. Peripheral S-T depression first appeared about fifteen minutes after S-T elevation was observed over the ischemic area. If reciprocal to S-T elevation, S-T depression recorded at the periphery would have occurred simultaneously with the S-T elevation which was recorded over the central part of the ischemic area almost *immediately* after ligation of the coronary artery.

Clinically, primary epicardial S-T depression may be recognized by comparing the size of S-T depression and S-T elevation from leads facing different aspects of the heart. The development of the shift in the S-T segment over a period of time should also make possible a distinction between primary and reciprocal S-T depression. If, for example, S-T depression increases without a corresponding change in S-T elevation (or even with a decrease in S-T elevation) it is obviously not reciprocal to the S-T elevation.

Degrees of Ischemia: The conclusion that S-T segment elevation is associated with more severe ischemia than S-T segment depression (based on experiments as reported here) seems to be contradicted by the observation that S-T depression never occurred immediately after ligation, that is, during the initial period before ischemia had become severe. In previous experiments in thirty dogs[9] it was noted that there was a 25 to 35 second delay in the appearance of S-T elevation after ligation of a coronary artery. If S-T depression is indeed related to a less severe degree of ischemia than S-T elevation, its absence during this initial period must be explained.

A theory based on cell metabolism may resolve this apparent discrepancy. Following ligation of the coronary artery the oxygen and glucose in the extracellular medium of the ischemic area become depleted. In previous investigations[9] it was demonstrated that one minute after ligation of the coronary artery the oxygen saturation of the blood in the corresponding coronary vein was reduced to less than 2 per cent. It may be assumed that at the same time the glucose content of the extracellular medium is also diminished, preventing increased potassium migration into the cell. It has been shown[9] that injection of a 5 per cent glucose solution (at a rate of 20 cc. per minute) into the coronary artery immediately after ligation results in S-T depression within a few seconds, probably due to the increased intra/extracellular potassium gradient. Conversely, ligation of the coronary artery without glucose supplementation results in a deficient glucose supply in the extracellular medium and we may assume that the shift of potassium into the cell cannot be increased. If there is no increase in the intra- and extracellular potassium gradient we may expect absence of S-T depression.

Releasing the tie on the coronary artery and permitting the flow of blood to return to the ischemic area is tantamount to increasing the oxygen and glucose supply in the extracellular medium. Consequently, glucose uptake is probably increased and potassium enters the cell, raising the intra- and extracellular potassium gradient. This may explain the transient S-T depression which often appears subsequent to the release of the tie on the coronary artery.

Under the conditions set up in experiment 4 one could expect the same pattern to prevail. When one of the sources of blood supply to the peripheral area was reopened the degree of

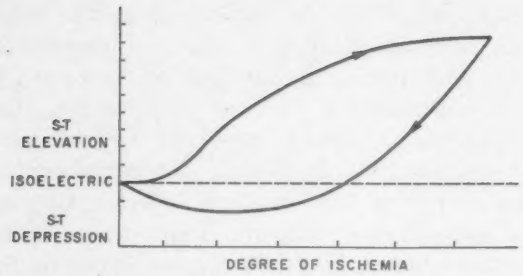


FIG. 12. Hypothetical pathways for development of ischemia and recovery. After initiation of ischemia there is a time lag of 25 to 35 seconds before S-T elevation occurs. As ischemia diminishes S-T depression appears. The diagram presents the hypothesis of these different metabolic pathways for development of ischemia and recovery from ischemia.

ischemia was diminished and S-T depression resulted. This applies also to the reappearance of S-T segment depression following transfusion and return to normal pressure (experiment 5B).

Metabolic Changes During Development of and Recovery from Ischemia: Observation of the time lags before appearance of initial S-T elevation and before return of transient S-T depression to the isoelectric line suggested the hypothesis that development of ischemia and recovery from ischemia may occur along different metabolic pathways (Fig. 12). From this diagram it may be seen that with increased blood flow S-T depression appears while there is still a considerable degree of ischemia. Thus, it is conceivable that there may be rare situations where S-T depression could occur with more severe ischemia than S-T elevation. At any rate, the state of cell metabolism appears to be of prime importance in influencing *degree* as well as *direction* of S-T segment response.

There have been many reports[18,19] indicating that the amount of stored glycogen and the reserve of high energy phosphates in the myocardial cell are relatively large. It therefore seems unlikely that S-T elevation beginning as early as 25 to 35 seconds after ligation could be due to a deficiency of cellular energy. Classical theory attributes this S-T elevation to cell injury, with resultant inability of the cell membrane to maintain the ionic gradient.[20] Accordingly, there would be leakage of potassium from the cell. However, experiment 2 furnishes evidence to the contrary. Even when ligation of the coronary artery was continued for as long as 30 minutes before releasing the tie, diminution of S-T elevation appeared within *one minute* and was in most instances replaced by S-T segment depression. During the next three to five minutes the S-T segment returned to the isoelectric line. Thus, it might be that S-T elevation occurring soon after occlusion of the coronary artery reflects reversible cellular injury but the cell membrane retains its functional ability. On the other hand, severe and prolonged ischemia will result in irreversible damage.

COLLATERAL CIRCULATION

The appearance of S-T depression from the periphery of the ischemic area (experiment 1) must be due to increased blood supply from collateral channels. The large cyanotic area which developed after ligation of the coronary artery diminished with the passage of time and the irregular, narrow reddish-blue patches which subsequently appeared along its margin shifted inward. Gregg[21] demonstrated increased collateral circulation in the femoral and carotid arteries shortly after occlusion; Wiggers[22] postulated the same in the myocardium. Other investigations[23] have shown that subsequent to acute coronary occlusion the blood flow to the ischemic area gradually improves. It would seem likely that collateral circulation is responsible for both the increase in blood flow to the ischemic area and the progressive diminution of its size. The appearance of primary S-T depression at the periphery of the ischemic area may also be due to collateral blood flow resulting in improved cell metabolism.

The effect of collateral circulation is further illustrated in experiment 4. When circuit A supplying the central area was closed, S-T depression was recorded at the periphery (area B) after fifteen minutes. When circuit B supplying area B was then closed, S-T depression disappeared and S-T elevation was recorded over this area. Subsequently, when circuit B was reopened S-T elevation disappeared after several minutes and S-T depression was again recorded from area B. This can only mean that peripheral S-T depression was produced by collateral blood flow to area B.

SUMMARY

1. Two types of primary S-T deviation, primary S-T depression and primary S-T elevation, have been observed clinically and demonstrated in experiments on animals.

2. Experiments in dogs demonstrated that S-T segment elevation is associated with more severe ischemia than S-T segment depression,

confirming clinical impressions in patients with myocardial infarction and/or angina pectoris.

3. Release of the tie on a large coronary artery resulted in reduced severity of ischemia; S-T elevation was diminished and in most instances replaced by transient S-T depression. This parallels clinical observations in patients during a severe attack of the variant form of angina pectoris.

4. Hemorrhagic hypotension following ligation of a large coronary artery resulted in further increase in S-T segment elevation over the cyanotic area and widely scattered "islands" of S-T depression appeared over both ventricles. S-T elevation over the cyanotic area decreased and the "islands" of S-T depression disappeared upon restoration of normal blood pressure. This illustrates the deleterious effect of shock in acute coronary occlusion and underlines the importance of maintaining adequate systemic blood pressure.

5. Primary S-T depression, as demonstrated in different experiments, occurs with ischemia and under nonischemic conditions due to chemical alterations. Primary S-T depression is in no way at variance with the principle of reciprocity or other fundamental laws of electrocardiography.

6. S-T segment depression and S-T segment elevation are due to two different types of cellular response.

7. The experimental findings suggest that development of ischemia and recovery from ischemia may occur along different metabolic pathways.

8. The effect of collateral circulation was studied by means of two artificial coronary artery circuits providing independent control of the blood supply to the central part of the ischemic area and its periphery. It was demonstrated that collateral circulation diminishes the extent and degree of ischemia simultaneously with the appearance of primary S-T depression from the periphery of the ischemic area.

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Historical Milestones

Description of Circulatory Collapse and Coronary Thrombosis in the Fifth Century A.D. by Caelius Aurelianus*

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IN CAELIUS AURELIANUS' book "On Acute Diseases and on Chronic Diseases"[1] one is astonished to find, as early as the fifth century A.D., a very detailed account of circulatory failure and a discussion of its causes. There are several reasons why succeeding generations of physicians failed to grasp these syndromes despite the title "Passio Cariaca." First, we have to blame this on the multiple meaning of some anatomic terms in antiquity and later times.

The word "cardiacus" is derived from the Greek word "kardia" which was used by the Roman physicians to refer to both the heart and stomach. This ambiguity was common in the time of Hippocrates (about 400 B.C.),[2] Galen[3] and Aretaeus[4] (second century A.D.), who wrote that this word indicated the upper ending of the stomach and the heart itself. These vague expressions have been perpetuated into modern times, e.g., the popular use of the word "heartburn" when we speak of hyperacidity. Ancient physicians were unable to relate pain around the precordium and upper epigastrium with any degree of certainty to either of these organs. Because of the impossibility of obtaining autopsies they were forced to deduce diagnostic considerations from observations on normal bodies, mostly of animals.

The chapters on "cardiac disease" by Caelius Aurelianus[5] demonstrate that the Roman author was faced with the same difficulties which any contemporary physician encounters unless he is aided by modern diagnostic methods. On purely clinical evidence it is often absolutely impossible to make a definite diagnosis of an acute disease of stomach, gallbladder or heart. To overcome his difficulties Caelius Aurelianus tried to correlate the previous literature with his own observations. He discussed alternate possibilities in a manner which reminds us almost of a presentation at a modern clinic.

The first chapter relating to heart disease bears the title, De Cardiacus. In a short introduction he confronts us at once with the difficulties of definition.[6] He states that some physicians use this term to designate a disease which has its seat in the stomach itself or in its upper ending and of which a griping pain appeared to be characteristic.[7] He further quotes that others understood cardiac disease as a serious condition manifested predominantly by weak pulse and sweating, or as we may say, by shock. Caelius Aurelianus intimated that some physicians adopted the name "cardiac" only to indicate the seriousness of the disease by an impressive word. "In our bodies the heart is unique and powerful and has the control of life."[8]

In the next chapter, What the Cardiac Disease Is, or How the Disease Is To Be Described,[9] Caelius Aurelianus quoted the famous Erasistratus of the Alexandrian school (310 to 250 B.C.)[10] who, at the early period, had already considered cardiac disease as an inflammation of the heart itself. Based on this concept, the first famous Greek physician in Rome, Asclepiades (born approximately 124 B.C.), had

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the idea that cardiac disease was due to a piling up, or stoppage, of the blood corpuscles.[11] This was a stroke of lucky intuition but without foundation by observation. We can not deduce from this idea that he understood the physiologic events in thrombosis or circulatory shock. One of the medical theories of his time was that all diseases could be explained by the narrowing or opening of the pores of the body, thus facilitating or slowing down the passage of the blood. Recent observations of the sludging of blood corpuscles in the capillaries during shock are a counterpart of this idea, but are based on painstaking photomicrographic studies. As so often happens, the intuition of the ancients was far ahead of their technical means and had no empirical background except for some occasional observations.

Circulatory Collapse

Caelius Aurelianus was not satisfied with a summary definition of cardiac disease as such. In the next chapter, by careful analysis of the so-called cardiac disease, he arrived at different clinical pictures. He first wrote of signs which appeared during or right after acute and severe fevers.[12] He observed as characteristic signs among those who already were afflicted or who threatened to die of cardiac disease, a very weak and rapid pulse which reminded him of little waves on the surface of the water. Apparently, he observed imminent vascular collapse resulting from atrial fibrillation. According to his exact description the pulse did not show any rhythm, but was not interrupted by pulseless periods. The pulse beats succeeded each other so fast and the little waves came so close together that he could hardly distinguish the single beats. As common in such cases of circulatory collapse, he observed thirst, nausea, light sleep and restlessness, and, as a sign of fatal outcome, coldness of the extremities. Occasionally, he encountered these symptoms after excessive loss of blood or severe diarrhea.[13] He also noticed, as abnormal features of some patients, a milk-white color, a flaccid and fatty appearance and a watery complexion.[13]

In other cases he observed, besides the empty and small waves of a fast pulse, a peripheral coldness which extended over the entire body and caused general numbness.[14] Toward the end when the condition worsened, the pulse became barely palpable[15] and respirations became "small and gasping and unbearably difficult."[16]

In many cases sudden, unexpected, profuse sweating occurred over the entire body, starting on the face and neck. He gave a very pertinent description of how the first thin sweat becomes more and more sticky and consistent, assuming a penetrant odor of water which had been used for washing raw meat. In this state patients were rarely able to speak and, if at all, only with a trembling voice. Their lips became pale, their eyes sunken and the thoracic movement heavy. The tongue sometimes remained moist but often appeared parched. Shortly before death their vision became dim, the extremities appeared cyanotic and the nails seemed to curve.[17] (This strange passage, taken out of its context, often has been considered as an observation of clubbed fingers, a conclusion which appears unjustified.) In most cases the mind was unimpaired until finally the circulation failed.

Fever: There is a lengthy discussion of fever as an essential factor of these instances of cardiac disease. Caelius Aurelianus concluded "that some patients with cardiac disease have no fever." Especially interesting is his observation that fever does not occur when cardiac disease is caused by excessive loss of blood.[18] It seems that the ancient physicians could determine the presence of fever fairly accurately, for Caelius Aurelianus wrote, "If one places one's hand in hollow and concealed parts of their bodies, or over the places where these patients have been lying, a considerable amount of burning may be felt, slowly and steadily rising from below. This sign, in connection with panting and the hot breath and a desire for cold drink, is indicative of fever. In some cases, too, the tongue is found to be dry and rough."[18] Adopting the theories of his teacher, Soranus, he believed that fever was not the cause of cardiac disease but was brought about by an assumed change in the state of the pores of the body, according to relative distance and arrangement of the atoms which were considered building stones of all tissues.[19]

The Organ Affected in Cardiac Disease

This general discussion of circulatory collapse turns again to a more specific inquiry in the chapter bearing the title, The Part Principally Affected in Cardiac Disease.[20] Caelius Aurelianus discusses in detail which part of the body should be considered the actual seat of cardiac disease. First he gives a resumé of the literature, in which Erasistratus is quoted because he

considered the heart as principally affected. Caelius Aurelianus then refers to other authors who were considering the pericardium, the diaphragm, adjacent parts of the lungs, the stomach and even the liver. Caelius Aurelianus insisted that,

> "the heart is found to palpitate in cases of this disease, and there is heaviness of the chest on the left side near the nipple . . . The disease is very serious, and this could not be the case unless some leading and especially important part of the body were affected. And the heart is a pre-eminently important part of the body and is vital to bodily health, furnishing, as it does, blood and pneuma to all other parts.[20]
>
> "In some cases of the cardiac disease there is heaviness of the whole chest and not merely of the left side. If that is true the disease may arise from an affection of the pleural membrane or of any other neighboring part of the body, if diseases must be assigned to particular parts."[21]

He disagrees with those authors who want to compare cardiac disease with injuries to the heart. In antiquity wounds of the heart apparently occurred frequently because of the particular types of combat practices. Most of these injuries led to immediate death. Caelius Aurelianus prefers to compare the cardiac disease to illness: "For if the heart is naturally constituted in the same way as the other parts of the body, it is necessarily subject to affections similar to those of the other parts."[22] He concludes that disease of the heart is not necessarily followed by death, in contrast to injury to the heart. Considering that "cardiac disease" could be the expression of a general disturbance of the body according to some of the theories of the contemporary Roman schools, he wrote,

> "To avoid becoming involved in the investigation of matters beyond our knowledge we certainly should refrain from arguing about the parts chiefly affected, for this question does not affect our understanding of either the indication or the treatment of the disease, since our remedies must be directed to the body in all its parts."[23]

Returning again to anatomic considerations, but without the foundation of postmortem examinations, he wrote that those patients who supposedly had an affection of the membranes surrounding the heart had repeated sharp piercing pains, whereas those with disease of the heart itself suffered mostly from a feeling of heaviness. However, since in both instances the parts near and around the heart were involved, he questioned the value of these symptoms for the final diagnosis.[24]

Differential Diagnosis of Stomach and Heart Disease

In the next chapter he tried to explain the differential diagnosis between cases of disease of the stomach or heart.[25] He discusses whether a strong or weak pulse, marked palpitation of the heart or the occurrence of a weak heart beat[26] (probably based on manual palpation) are of diagnostic importance. Although his conclusions are somewhat contradictory he appears inclined to assume a weak heart beat, heaviness in the chest and a choking sensation as significant of morbus cardiacus.[25,26] On the other hand, he regards pain between the shoulder blades, salivation, vomiting and heaviness after meals as indicative of disease of the stomach.[26,27] However, "if both diseases occur at the same time, it is more difficult to make a reliable distinction between them, but that is no obstacle to treatment, for both diseases are treated by the same procedures."[28] "For we do not vary our treatment according to the differences in the antecedent causes."[29]

Since currently we consider the constitutional and environmental factors of heart disease, we should not omit mentioning that Caelius Aurelianus observed a constitutional disposition to heart disease. He was aware of precipitating factors of such attacks.

> "The disease occurs more often in summertime, in men rather than in women, in warm young bodies, and in those that are full-figured and athletic. And the antecedent causes which give rise to this disease are many and varied. The usual causes, however, are continual indigestion, excessive drinking of wine, bathing after taking food, vomiting after dinner, and grief or fright in which the body is sympathetically affected and dissolved in sweat."[30]

Angina Pectoris and Coronary Thrombosis

Caelius Aurelianus was apparently aware that an independent syndrome of precordial pain existed. He mentioned it separately from the picture of circulatory collapse or sudden onset of arrhythmias. He wrote at the conclusion of his treatise on cardiac disease, "There is also a disease called by some Cardimona (Greek Cardiogmos). In this disease there is always pain at the mouth of the stomach, a condition which many laymen call pain of the heart."[29] (The word Cardiogmos comes from the Greek

word "cardia" meaning heart and "ogmos," crying out for pain.) It is suggestive that this quotation refers to angina pectoris in the sense of Heberden. In the eighteenth century, Heberden[31] described in detail angina of effort and decubitus. He did not give an account of circulatory collapse as Caelius Aurelianus had done, or a detailed differential diagnosis of heart disease. This is remarkable because in a footnote he referred to the passage of Caelius Aurelianus on pain in the chest. According to Heberden, no other ancient author had mentioned this syndrome.[31]

To summarize, Caelius Aurelianus gave an excellent description of circulatory collapse in connection with febrile diseases. He also seems to have observed cases of shock which accompany the acute onset of atrial fibrillation. He discussed the possible differentiation between primary disease of the stomach or heart. The cardinal symptoms of acute coronary thrombosis also can be found in these chapters: precordial heaviness,[19] pain[23,32] (especially in the left side near the mamilla), the choking sensation,[25] the collapse with clear mind and poor prognosis.[32]

He was guided by his clinical instinct and the knowledge of earlier writers. He left us a more detailed description of his observations than any other medical writer of antiquity. Aretaeus was probably a more dramatic writer, but not as good a teacher as Caelius Aurelianus. Because his excellent description of cardiac syncope must have been familiar to Caelius Aurelianus since it was given 300 years earlier, it should be quoted here:[33]

> "How appropriately has the physician, how justly has the public voice named this disease 'the quick destroyer.' For what can be more powerful or more rapidly fatal than syncope? What other name could be more expressive to describe its effects? What part is more important than the heart in its influence on life and death? And there is no improbability in syncope being a disease of the heart or an injury to the power of life which resides in it, such is its destructive rapidity, and such its form; for the disorder, being inimical to the human constitution, consists in a loosing of the bonds of vitality, on which when the disease has once laid its fangs, it quits not its hold until it consigns the body to dissolution. And when the bonds of the constitution are loosed, we have syncope: then perspiration is profuse on every part of the body . . . cold, with a copious moisture about the nostrils; the patients are parched with thirst; for when all other parts are dried up, so are especially the organs that produce thirst, the esophagus and mouth; . . . the mind is serene, every sense clear, the understanding subtle, the judgment prophetic, for the patients see in the first place, that their end is approaching, and then they predict to the bystanders coming events. Some times people think them talking deliriously; but when their predictions come to pass, are amazed."[34]

Therapy of Cardiac Disease

If Caelius Aurelianus devoted many chapters to diagnostic discussions, he still filled more pages with therapeutic advice. His common sense in the therapy of cardiac disease is remarkable. It is impossible to go into the endless and often unnecessary details. Caelius Aurelianus scorned those who declared cardiac disease as incurable and left their patients unattended. He advised the maintenance of a moderate room temperature by fanning and sprinkling of cold water; and using the odors of pine and other extracts to create an agreeable air. He recommended light bed clothes, mattresses not too soft or too hard and a wide bed. "Thus, while the patient is lying on one side of the bed, we can arrange the bedding on the other side. For when the patient has to be carried repeatedly from one bed to another he becomes exhausted and his illness is aggravated even from this little movement." This is similar to our orders for "coronary care." He continues: "Now bandage and bind the patient's limbs, though not very tightly, and have him cease not only from bodily activity, but if possible also from mental concern."[35] This is better than tourniquets now used against shock to keep the circulating blood from stagnating in the peripheral vessels. He further advised the use of cool sponges and dusting powders against sweating, and also anointing with balsams of different sources. He chose these according to their expected astringent or loosening effect on the pores of the body conforming to the prevailing theory of diseases. But despite the strong influence of such deductive reasoning his practical sense formed his judgment in therapeutic matters. He strongly advised against the use of drawing plasters on the precordium.[36] He decried the use of hot [37] or cold baths,[38] of clysters except in cases of constipation[39] and of passive exercises,[37] and he called the use of venesection as "no different from murder by cutting the throat."[38] He gave many details about the diet and the

use of various brands of wines. His suggestions amount to what we would call a soft or bland diet. Discussion of other details of this extensive treatise would require a knowledge of the daily habits of the Roman upper class. He concludes his chapter on therapy with the words: "And if any success attends the application of the aforesaid remedies, let the repairing of the body continue until it is as complete as required."[40]

ACKNOWLEDGMENT

Permission for quotation from this work has been given by the author and the publisher, for which I want to express my thanks.

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12. C.A. Translation II, 165. Chapt. 32: How to recognize those who may lapse into the Cardiac Disease and those who already have the disease.
13. C.A. II, 166.
14. C.A. II, 167.
15 C.A. II, 167. For "formicabilis" cf. Galen, lib. de puls. ad tirones VI.
16. C.A. Translation II, 167.
17. C.A. II, 168.
18. C.A. Translation II, 179. Is Fever Present in the Cardiac Disease?
19. C.A. II, 176.
20. C.A. Translation II, 180.
21. C.A. Translation II, 181.
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23. C.A. Translation Dr. II 183
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Case Reports

Congenital Heart Disease Associated with Congenital Hypofibrinogenemia

Report of a Case Subjected to Corrective Surgery*

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CONGENITAL BLOOD DYSCRASIAS of the coagulation deficiency type are not included in the list of developmental defects frequently associated with congenital heart disease. A review of the American literature reveals no instance of congenital heart disease occurring in association with afibrinogenemia or hypofibrinogenemia; one case was suggested but not proved to be either cardiac or coagulation defect.[1] Pritchard and Vann,[2] reviewing the literature on congenital afibrinogenemia in 1954, stated there was only one case of associated developmental anomaly: hair lip and cleft palate.

We are reporting a patient with congenital hypofibrinogenemia and congenital heart disease (pulmonic stenosis and partial anomalous pulmonary venous drainage) who was successfully subjected to correction of the pulmonic stenosis. To our knowledge, this is the first reported case of this nature.

CASE REPORT

A. S., a twelve year old white boy, was first admitted to the Kings County Hospital in 1955 with poorly controlled hemorrhage following tooth extraction. Hematologic history was limited although it was noted that there had been "bruising and bleeding very easy" since early childhood. There was a history of asymptomatic heart murmur, also dating to early childhood, but no history of rheumatic fever. The cardiac murmur was described as that of pulmonic stenosis. An incidental finding was left pyelonephritis which was treated; cardiac catheterization and angiocardiography were performed (Table 1). The findings were interpreted as atrial septal defect and infundibular pulmonic stenosis.

In July 1958 he was readmitted because of fatigability and failure to grow. There was no definite history of cyanosis. Family history did not reveal parental consanguinity. There was a history of "easy bruising and bleeding" in two members of the family. The clotting time was prolonged with poor clot retraction. Genitourinary studies revealed minimal left hydronephrosis but the function was satisfactory. Liver profile was normal. Cardiac catheterization data, presented in Table 1, revealed that the right ventricular pressure was almost double that noted in 1955; septal defect could not be demonstrated; the step-up in oxygen content in the "high right atrium" suggested partial anomalous pulmonary venous drainage.

The next admission was two months later, on September 29, 1958. *Physical examination* revealed a well nourished, well developed male adolescent who was undersized, weighing 32.6 kg. Blood pressure was 120/70 mm. Hg, pulse 76 per minute, respirations, 18 per minute. Giant A waves were noted in the jugular veins. The lungs were clear. The apical impulse was in the fifth intercostal space just lateral to the left midclavicular line. There was a harsh pansystolic murmur loudest at the left sternal border in the second and third interspaces and widely transmitted. A systolic thrill was palpable at the pulmonic area and was transmitted to the left side of the neck, toward the left shoulder and along the left sternal border. P_2 was questionably split.

The electrocardiogram revealed mild right ventricular strain. Chest x-ray films demonstrated poststenotic dilatation of the pulmonary artery, right ventricular enlargement and slightly decreased vascularity of the lung fields (Fig. 1). Kidney and liver function tests were within normal limits.

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TABLE I
Catheterization Data

Location	Pressures (mm. Hg)			O_2 Content (vol. %)		
	1955	1958	1959	1955	1958	1959
Inferior vena cava	...	...	...	10	11	...
Superior vena cava	...	...	...	9	9.6	...
Right atrium				11	...	...
High	...	...	...	...	11.2	...
Mid	...	3	7	...	...	...
Low	...	...	...	...	9.5	...
Right ventricle	52/12	95/3	61/8	...	10.4	14.1
Pulmonary artery	20/10	12/6	22/10	...	10.4 (71% saturation)	14.1 (78% saturation)
Brachial artery	...	128/80	120/74	...	13.4 (92% saturation)	17.3 (94% saturation)

Hematologic evaluation showed that the Rumpel-Leede phenomenon was negative; there was normal bleeding time, prothrombin consumption and thromboplastin generation; platelets were over 200,000 per cu. mm.; prothrombin time was slightly increased. The clotting time was twenty-two minutes (Lee-White) with poor clot retraction and marked fragmentation. Plasma fibrinogen level was 40 mg. per 100 ml. (normal range is 200 to 475 mg. per cent; values less than 180 mg. per cent are considered to be definitely pathologic). Hemoglobin was 14.5 gm. A diagnosis of congenital hypofibrinogenemia was considered.

Surgical Treatment and Findings: It was decided that the patient should be subjected to pulmonic valvotomy if there were a satisfactory response to fibrinogen therapy. The patient received 1 gm. of fibrinogen infusion daily from October 8 through October 14, 1958. The clotting time on October 13 was seven minutes. The plasma fibrinogen level immediately preoperatively was 180 mg./per 100 ml. and the clotting time six minutes.

FIG. 1. Preoperative x-ray film of the chest.

FIG. 2. X-ray film of the chest obtained fourteen months after operation.

On October 15, 1958, the patient was subjected to surgery under hypothermia (31° to 32°c.). Attention was directed to meticulous hemostasis. Examination of the heart confirmed the diagnosis of pulmonic valvular stenosis. The right atrium was explored digitally through its appendage; anomalous venous drainage from the right middle lobe was discovered but no septal defect palpated. Inflow and outflow occlusions were accomplished and the classic dome-shaped valve of congenital pulmonic stenosis was incised to the annulus by three radial incisions through a supraventricular incision in the pulmonary artery. Digital exploration of the right ventricle revealed concentric outflow hypertrophy but no true infundibular stenosis.

Infusion of fibrinogen was maintained slowly from the time of incision of the skin. No abnormal bleeding was noted until immediately following valvotomy. Clotting time just prior to inflow occlusion was seven minutes; no significant fragmentation of the clot was noted. During repair of the pulmonary arteriotomy a generalized ooze became apparent and the mediastinal tissues appeared to be suffused with blood. Fibrinogen was administered rapidly. The hemorrhagic ooze subsided after a total of 5 gm. was absorbed; however, correction of the anomalous venous drainage from the right middle lobe was deemed too hazardous. A sixth gm. of fibrinogen was administered slowly. Intrapleural catheters were placed and the wound was closed.

Postoperatively the anemia was corrected; no further fibrinogen infusion was necessitated. Platelet determinations remained within normal limits. The patient was discharged three weeks later.

Postoperative Findings: The patient was readmitted in December 1959, fourteen months postoperatively, for cardiac re-evaluation. He was asymptomatic, claiming exercise tolerance comparable to that of his friends. Weight was 36 kg., a gain of 3.4 kg.; there was a gain in height of about 2 cm. A phonocardiogram revealed that the pulmonic component of the second sound followed the aortic by 0.04 second (preoperatively it was 0.08 second). The electrocardiogram revealed an axis of 100°, as compared with 120° preoperatively. Catheterization data are presented in Table 1. The right ventricular hypertension, although diminished, persisted. It suggested infundibular stenosis or outflow hypertrophy aggravated by the small left to right shunt from the partially anomalous pulmonary venous drainage (Fig. 2).

Comments

Congenital afibrinogenemia is a rare disease. There are twenty-six reported cases.[3] It is characterized by an absence of circulating fibrinogen. Men are afflicted predominately in ratio of 2 : 1. Consanguinity of parents and/or grandparents occurs in about one-third of the cases. Hemorrhagic diathesis in the relatives of seven patients has been reported. Bleeding time is variable but frequently within normal limits; sedimentation rate is low in about half the cases; platelets are usually normal; clotting time is markedly prolonged and if a clot is formed it fragments completely.[1-4] Although hemorrhage is a prominent feature, usually dating from a very early age, it is a lesser problem than in hemophilia.[2] It is evident that coagulable blood is not essential for at least some degree of hemostasis.[4,5]

"Constitutional hypofibrinogenemia" has been described.[3,6] It is characterized by extremely low plasma fibrinogen levels, bleeding gums, purpura, moderate thrombocytopenia and normal bleeding and clotting times. A total of five cases are cited.

Acquired fibrinogenopenia is widely reported. The multiple etiologic diseases are the following: (1) cancer, especially prostatic, when there is metastasis[2] of the bone marrow and bronchogenic carcinoma[7]; (2) liver and biliary disease[2,6,8]; (3) certain obstetric emergencies such as abruptio placenta, amniotic fluid infusion or the dead fetus syndrome[9,10]; (4) following massive transfusions, particularly in surgical patients[9]; (5) cyanotic heart disease[11,12]; (6) hemolytic anemia[2]; and (7) "purpura fulminans."[2] Phillips et al.[9,10] have postulated that hypofibrinogenemia in surgical and obstetric patients results from either hydrolysis by a fibrinolysin activated by tissue extracts or from deposition as fibrin emboli. Because of the presence of fibrinolysin and active proteolytic enzymes[13] in the plasma of surgical patients, levels of plasma fibrinogen higher than 100 to 150 mg. per 100 ml. (usually considered minimal for hemostasis)[3] may be required in patients undergoing extensive surgery.[9]

It is estimated that 100 mg. of fibrinogen per kg. of body weight will raise the plasma concentration of an afibrinogenemic patient to approximately 200 mg. per 100 ml.[12] The level rises promptly; however, only one-half remains after forty-eight hours.[14] During an operative procedure, our experience has convinced us that the dosage of fibrinogen is best judged empirically by the hemostatic response of the wound surfaces.

The incidence of congenital hypofibrinogenemia is not known. Its characteristics, other than low plasma levels of fibrinogen and prolonged clotting time, have not been defined. Wintrobe[3] mentions the entity of congenital

hypofibrinogenemia; however, he does not elucidate whether it is a totally different disease or just a less severe form of afibrinogenemia. Traces of fibrinogen have been detected in the plasma of at least two cases of congenital afibrinogenemia, utilizing immunochemical methods.[14] Pritchard and Vann[2] state that congenital afibrinogenemia must be differentiated from hypofibrinogenemia and cite four cases of hypofihrinogenemia occurring in relatives of the parents of patients having afibrinogenemia. Schulman and Currimbhoy[12] observe that "congenital hypofibrinogenemia apparently also occurs." The case herein reported is similar to recorded cases of congenital afibrinogenemia, confirmed by the history of bleeding tendency in early childhood and the absence of those diseases which have been known to predispose to acquired hypofibrinogenemia. Cyanosis was never noted while our patient was in the hospital or clinic and there was no record of polycythemia.

In the case reported, it was our opinion preoperatively that surgical correction for the anomalies should be undertaken under direct vision, particularly because atrial septal defect remained a possibility. The use of cardiopulmonary bypass technic would necessitate the use of heparin, a potent anticoagulant. Hemorrhagic diathesis occasionally occurs during and immediately after surgery performed under hypothermia.[15] Impairment of coagulation, primarily, is uncommon. For this reason, we believed that hypothermia and occlusion of inflow would be the procedure of choice. The anomalous venous drainage was not corrected because the risk, at the time, was too great in view of the small shunt that remained.

Summary and Conclusions

A case of congenital hypofibrinogenemia with associated congenital heart disease successfully subjected to operative correction of the major defect is presented. Hypothermia with occlusion of inflow in our opinion, is the procedure of choice in cases of severe coagulation deficiencies when the cardiac defect is of a type amenable to this technic.

Bleeding and clotting times, as scanning tests, should be performed on all patients on whom extensive surgery is anticipated; however, it must be stressed that a detailed history and thorough physical examination may evoke suspicion of those hemorrhagic syndromes in which values for these two tests are within normal limits.[16] In this way coagulation deficits may be discovered, the exact factor at fault determined and surgery planned accordingly.

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Cor Triatriatum

Successful Diagnosis and Surgical Correction in a Three Year Old Girl*

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COR TRIATRIATUM, as its name implies, involves a third atrial chamber. In the majority of cases this chamber represents a dilated common pulmonary vein with a stenotic orifice communicating with the left atrium proper (often and more descriptively termed "stenosis of the common pulmonary vein"). Other variants grouped under cor triatriatum include cases with anomalous bands in the left atrium or an accessory septum in the right atrium. Niwayama[1] recently reviewed in detail thirty-eight cases of stenosis of the common pulmonary vein including five of his own, and presented a classification based on the size of the opening in the intra-atrial septum and on patency and location of the foramen ovale.

Cor triatriatum in adult patients has been successfully corrected,[2–5] including one patient from this hospital,[6] but no references to successful diagnosis and correction in children have been encountered. Gousios and Cotton[7] described a two year old girl with coarctation of the aorta and an additional defect suspected of being either congenital mitral stenosis, a congenital band across the atrium or an underdeveloped left ventricle; postmortem examination demonstrated coarctation of the aorta and a constrictive band (cor triatriatum).

The following case report constitutes a typical, severe case of cor triatriatum in a young child, successfully diagnosed and surgically corrected, and is presented together with preoperative and postoperative right heart catheterization data.

CASE REPORT

This three year old girl was referred by her family physician for cardiac evaluation on March 3, 1959. A heart murmur had been heard two months earlier when she was hospitalized with pneumonia. In retrospect, the parents thought the girl always tended to have a rapid heart rate and heavy respirations and tired more easily than her playmates. In addition, duskiness of the lips had been noted two months prior to pneumonia. The child had always had frequent upper respiratory infections and for six months had been treated for anemia. Another feature, one not appreciated until after surgery, was her general irritability. The parents and two siblings were in good health.

On examination, she appeared chronically ill, with pallor and questionable mild cyanosis. Weight was 25½ pounds and height was 36 inches. There was minimal precordial bulge. Lungs were clear to auscultation. Cardiac activity appeared increased but no thrills were palpable. A grade 2 systolic murmur of medium pitch and nonspecific quality was heard at the apex. The second heart sound was broad (questionably split) and greatly accentuated over the pulmonic area. Blood pressure was 90/50 mm. Hg in the right arm and 90/56 mm. Hg in the right leg. The liver was palpable 3 cm. below the right costal margin but was not tender to palpation.

Roentgenograms (Fig. 1) revealed moderate cardiomegaly, with apparent left atrial enlargement and pulmonary vascular markings that were slightly increased. Whether this increase in vascular markings was primarily venous or arterial could not be determined. The *electrocardiogram* (Fig. 2) exhibited right axis deviation and marked right ventricular hypertrophy.

Catheterization Findings: The clinical impression was severe pulmonary hypertension, secondary to a left to right shunt or left-sided disease. Right heart catheterization was performed on April 17, 1959, and revealed severe pulmonary hypertension and a markedly elevated pulmonary wedge pressure (mean of 35 mm. Hg), with no evidence of left to right or right to left shunts (Table 1). *Selective*

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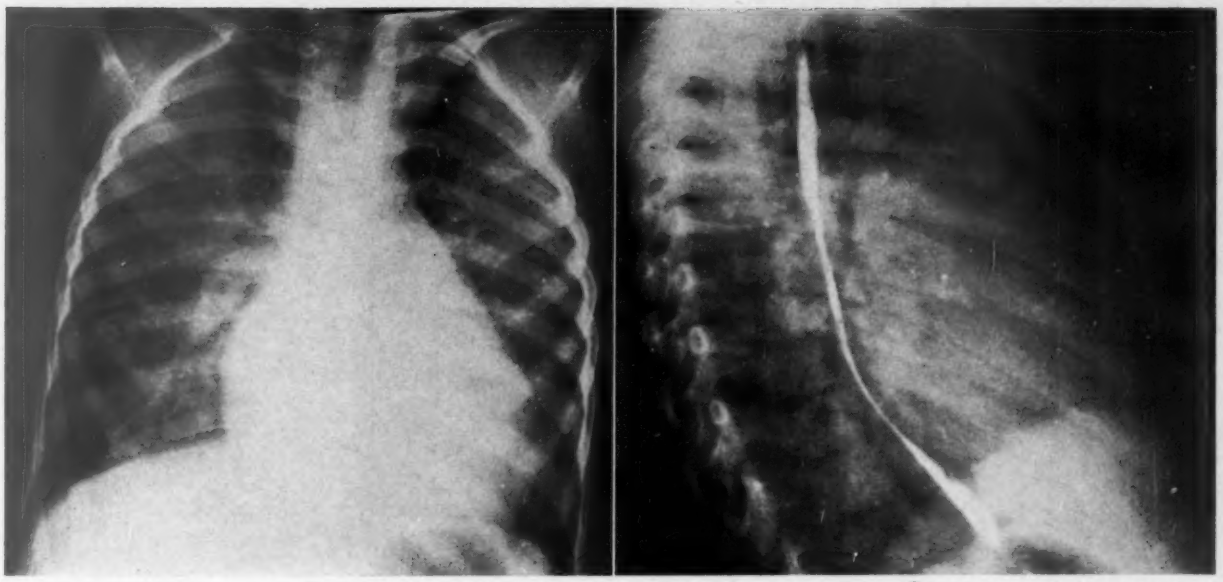

A B

FIG. 1. Roentgenogram taken on March 3, 1959. Patient was three years of age. A, posteroanterior view. Note mild cardiomegaly and mild prominence of pulmonary vascular markings (venous). B, lateral view. Note mild posterior displacement of esophagus, suggesting some degree of left atrial enlargement.

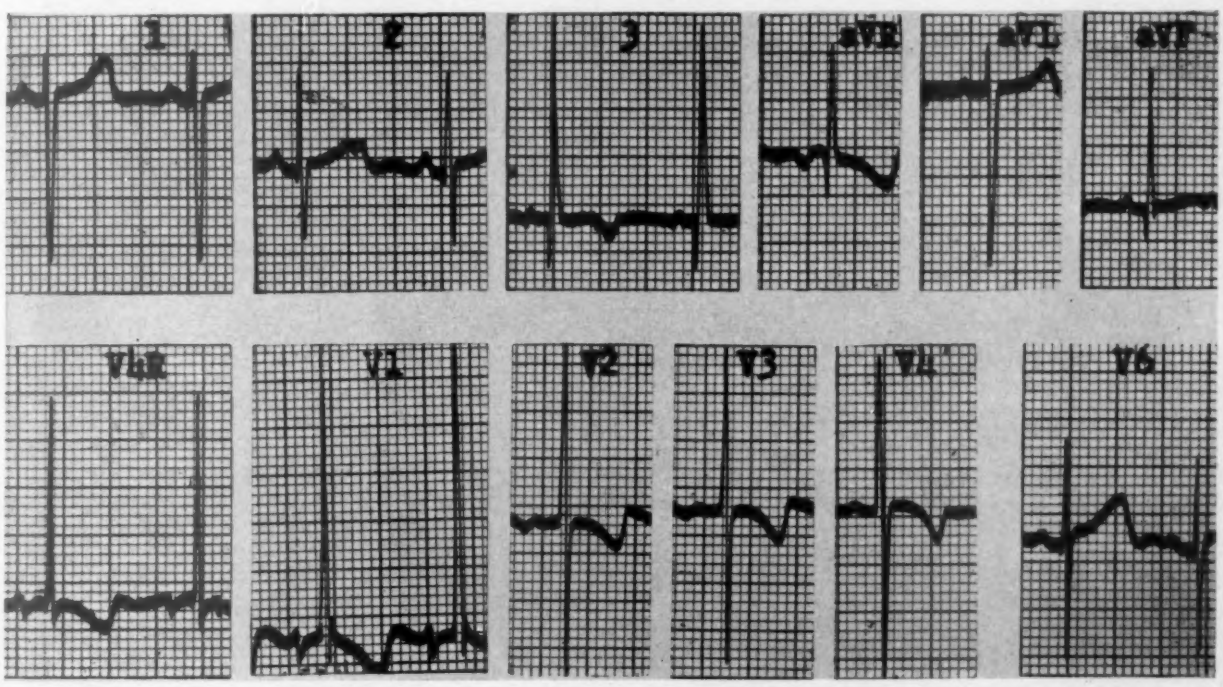

FIG. 2. Electrocardiogram taken on March 3, 1959. Patient was three years of age. Note right axis deviation and marked right ventricular hypertrophy (high voltage R waves in leads V_4R and V_1, with inverted T waves from lead V_4R to V_4).

angiocardiography was performed from the right ventricle. The opaque medium took an essentially normal course through the lungs and left side of the heart, except that the pulmonary veins appeared to be entering the left atrium more medially and superiorly than usual. However, opacification of the pulmonary veins was not adequate for critical interpretation.

Surgical Findings: On the basis of these findings a diagnosis of cor triatriatum was made The only disturbing feature was the presence of apparent left atrial enlargement on the roentgenogram (Fig. 1B). However, this enlargement was considerably less than would be expected from a mitral lesion with comparable pulmonary hypertension at this age. Surgery was performed on August 4, 1959, using

TABLE 1
Right Heart Catheterization Data

Location	Pressure (mm. Hg)	Oxygen Content (vol. %)	Oxygen Saturation (%)	
			Van Slyke	Oximetry
Preoperative: April 17, 1959				
SVC	...	10.2	68	69
IVC	...	...	..	54
RA	10/5 (6)	...	..	69
RV*	85/0/5	...	..	64
PA*	85/34 (60)	9.8	65	65
PA wedge	38/33 (35)	...	..	...
FA	...	14.8	97	98
Postoperative: May 2, 1960				
SVC	...	...	..	63
RA	7/4 (6)	...	..	73
RV	39/0/3	...	..	78
PA	34/12 (20)	13.1	72	73
PA wedge	9/7 (8)	...	..	...
FA	...	18.0	99	100

* Radioactive methyl iodide inhalation tests were negative for left to right shunts, sampling being taken from the pulmonary artery and the right ventricle.

cardiac bypass. The pulmonary veins were found to be very tense. They drained into a third atrium, which in turn communicated with the left atrium proper through a 5 mm. opening. The septum between this third atrium and left atrium proper was surgically excised under direct vision. No other cardiac abnormality was present.

Postoperative Course: Dyspnea and cyanosis were present postoperatively, and on the fourteenth postoperative day severe right heart failure developed. This responded to medical measures and the patient was discharged from the hospital on the twenty-sixth postoperative day with good color and no signs of cardiac failure. The pulmonic component of the second heart sound was still very prominent at this time. In the next three months the patient did exceedingly well, and was described by the parents as an entirely different girl who was now happy and playful. She had gained 5 pounds in the interim. The administration of digitalis had been discontinued. On physical examination cardiac activity was normal, with no murmurs and only minimal accentuation of the pulmonic component of the second sound.

Follow-up Examination: She was rehospitalized on May 2, 1960, for repeat right heart catheterization. Her health had been excellent and she had gained

Fig. 3. Postoperative roentgenogram taken on May 3, 1960. Patient was four years of age. Posteroanterior view. Cardiac size about normal.

an additional 5 pounds (weight now 37½ pounds and height now 40 inches). No murmurs were heard and the second heart sound showed normal variable splitting and normal intensity of its pulmonic component. Roentgenograms revealed borderline cardiomegaly and normal pulmonary vascular markings (Fig. 3). The electrocardiogram (Fig. 4) continued to exhibit right ventricular hypertrophy but of a much lesser degree. Right heart catheterization demonstrated a normal pulmonary wedge pressure (mean of 6 mm. Hg) and minimal residual elevation in pulmonary artery and right ventricular pressures (Table 1). No shunts were found.

COMMENTS

Although cor triatriatum is a relatively rare cardiac defect, it is a correctable malformation, and as such deserves particular emphasis. The majority of patients die within the first two years of life.[1] Therefore, if these lives are to be salvaged, early diagnosis and treatment are mandatory. The severity of clinical symptomatology is related to the size of the stenotic orifice, and the symptoms are those of pulmonary venous and arterial hypertension.

In patients with a small orifice, symptoms appear in early infancy, progress rapidly and death often occurs within several days or weeks. Dyspnea, feeding difficulties and failure to thrive are the principal features.[8] In two or three year old children anorexia and irritability may be present. In older children,

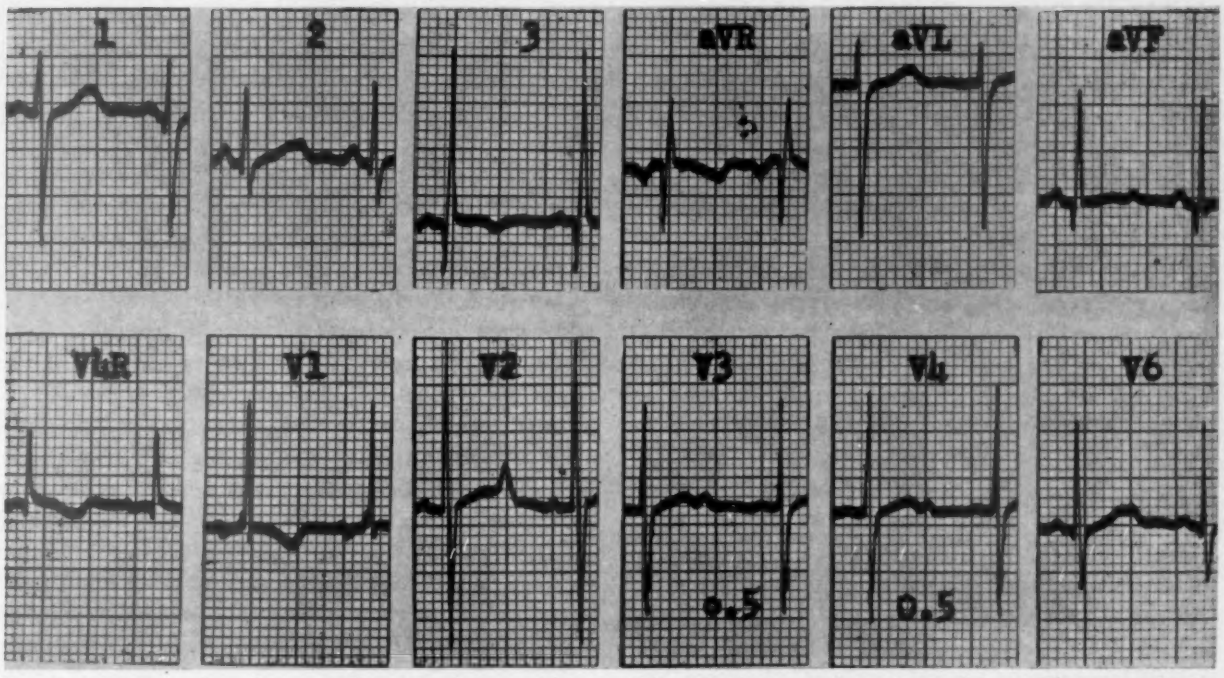

FIG. 4. Postoperative electrocardiogram taken on May 3, 1960. Patient was four years of age. Right ventricular hypertrophy still present, but less striking. T waves now positive from lead V_2 to V_6.

cough and "pneumonia" (pulmonary edema) may occur initially. Dyspnea typically occurs in persons of all ages and is often the only symptom in older children and adults with a larger orifice. In severe cases growth retardation is demonstrated as are signs of pulmonary edema (rales) or right heart failure (hepatomegaly, peripheral edema, cyanosis). A precordial bulge may occur if there is considerable cardiomegaly. Although murmurs frequently are present, they are variable in time, quality and location; the only consistent auscultatory finding is an accentuated pulmonic component of the second sound.[8] On roentgenograms cardiomegaly is demonstrated, mainly right ventricular, and roughly proportional to the degree of symptomatology. The pulmonary vascular markings are prominent, but their primarily venous nature may not be recognized. Although typically not enlarged, the left atrium may sometimes appear prominent[1] (as in the case presented herein). Right ventricular hypertrophy and right atrial enlargement (peaked P waves) are the typical electrocardiographic findings, and these may correlate with the degree of stenosis.[8] At right heart catheterization, there is pulmonary hypertension with elevated pulmonary wedge pressure; if measured, left atrial pressure will be found to be normal. Selective angiocardiography from the right ventricle or pulmonary artery should be helpful, but reports of its use in this defect are lacking. In the present case angiocardiography was only of limited help due to poor detail. In one of Niwayama's cases[1] death occurred in an infant immediately after the injection of opaque medium in the pulmonary artery, suggesting caution in the use of this technic.

Differential Diagnosis: Cor triatriatum in older children and adults should be identified relatively easily, since the clinical picture will have had time to resolve itself into a fairly stereotyped pattern with the features described previously. Differentiation from primary pulmonary hypertension and pulmonary hypertension associated with shunts is accomplished by the demonstration of a high pulmonary wedge pressure. An enlarged left atrium will nearly always be present in older patients with elevated wedge pressures secondary to mitral valve abnormalities.

In infants the differential diagnosis presents great problems, and the patient may even be initially viewed as having a pulmonary rather than a cardiac problem. *Congenital mitral stenosis* generally produces only a systolic murmur in infants and involves no left atrial enlargement.[9] Cardiac catheterization findings may be similar, except that left atrial pressure will be elevated if this measurement can be made. Congenital mitral stenosis commonly has an associated patent ductus arteriosus or

aortic stenosis. *Endocardial fibroelastosis* generally produces a pattern of left ventricular hypertrophy on the electrocardiogram, but the rare case of right ventricular hypertrophy and pulmonary hypertension may present difficulties in diagnosis. However, such cases should have appreciable left atrial enlargement. Infants with *total anomalous pulmonary venous connection* in whom the systemic connection is rudimentary or exceedingly long (as with infradiaphragmatic connection) will present the picture of pulmonary venous obstruction also, but cyanosis tends to be more prominent in these patients.

Cases with *associated atrial septal defect* may have variable findings.[1] If a defect or patent foramen ovale is located between the extra chamber and right atrium, a left to right shunt will occur. A widely patent foramen ovale or defect between the lower left atrial chamber and right atrium may permit a right to left shunt, with clinical cyanosis. In related cases with a completely obstructed pulmonary vein but anomalous systemic venous connections, the picture will be that of total anomalous pulmonary venous connection. Of these, those patients with small or rudimentary systemic connections will have signs of intense pulmonary obstruction and will show gross cyanosis. Cor triatriatum may occur in combination with other cardiac anomalies, with further alteration in the clinical and laboratory findings.

In patients of any age, the presence of pulmonary hypertension should alert the clinician to the possibility of cor triatriatum. The finding of an elevated pulmonary wedge pressure is highly suggestive of the defect, and if combined with a normal left atrial pressure, is pathognomonic.

Surgical exploration for cor triatriatum defect is advisable in all patients with a greatly elevated pulmonary wedge pressure, particularly if left atrial size appears near normal.

Summary

Successful diagnosis and surgical repair of a cor triatriatum defect (stenosis of common pulmonary vein) in a three year old girl is described. Prior to surgery severe pulmonary hypertension was found at right heart catheterization, with a mean pulmonary artery wedge pressure of 35 mm. Hg. Nine months after surgery there was a normal mean pulmonary artery wedge pressure of 6 mm. Hg. Except for a transient but severe episode of cardiac failure in the immediate postoperative period, the patient showed an excellent response to surgery.

This case illustrates the typical clinical features of cor triatriatum as seen in young children. The symptoms and signs are those of pulmonary venous and arterial hypertension, and are related to the size of the stenotic orifice. Dyspnea is a central feature in persons of all ages. The majority of patients die within the first two years of life, often after a relatively short period of symptoms. In such cases differentiation from congenital mitral stenosis, endocardial fibroelastosis, anomalous pulmonary venous connection or primary pulmonary disease may be difficult. However, at any age, clinical evidence of pulmonary hypertension and the finding of an elevated pulmonary artery wedge pressure are highly suggestive; and if associated with normal left atrial pressure, are pathognomonic for this anomaly.

Although comparatively rare, cor triatriatum is easily and completely corrected by surgery and therefore deserves particular emphasis. Surgical exploration for this defect is justified in patients with high pulmonary artery wedge pressure and near normal size of the left atrium.

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Ventricular Tachycardia Responding Solely to Digitalis Therapy*

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RECENT ARTICLES HAVE revived interest in the question of the advisability of the administration of digitalis in ventricular tachycardia.[1,2] QRS aberration in supraventricular tachycardia occurs frequently and may make differentiation from ventricular tachycardia an electrocardiographic problem. Resolution often depends upon demonstrating conducted atrial beats. Recognition of atrial activity in paroxysmal tachycardia may be difficult in routine electrocardiographic leads. Frequently such activity may be demonstrated in the electrocardiogram by special procedures as carotid sinus pressure or special leads such as esophageal leads designed to expose such activity. The distinction between supraventricular and ventricular tachycardia is of more than academic interest. It is essential in outlining therapy and evaluating prognosis.

Digitalis is indicated in supraventricular tachycardia; quinidine or procaine amide in ventricular tachycardia. However, the rigidity of this therapeutic doctrine is not absolute. Some authors have revealed that digitalis produces conversion of ventricular tachycardia in desperate cases.[3] Others have not noted any detrimental effect when the drug has been given concurrently with other agents.[4] Exact diagnosis of the arrhythmia has not always been available in cases reported to respond to digitalis.

The following is a well documented case of ventricular tachycardia treated solely with digitalis.

CASE REPORT

A sixty year old man was admitted to the accident ward at 4:00 A.M. with a chief complaint of shortness of breath and rapid heart beat. He stated that he had been well until four days ago when he had returned home from work during the morning with a feeling vaguely described as "being sick." The evening of that day he had noted the onset of fever with chills and shortness of breath. During the night he experienced an abrupt change in the rate of his heart; it became quite rapid. During the next days a cough productive of yellow sputum with occasional blood streaks developed and he continued to have chills and fever. He had some epigastric pain associated with and worsened by the cough and had vomited a clear fluid several times. He had received injections of antibiotics by his physician without benefit. The rapid heart rate had not changed, according to the patient's observation, up to the time of his hospital admission.

Examination revealed an acutely ill man with a temperature of 102°F., and pulse over 200 per minute and respirations of 40 per minute. There was moderate but not marked cervical venous distention which disappeared when he sat on the edge of the bed. The blood pressure was 90/70 mm. Hg. The heart was slightly enlarged on examination and demonstrated the tachycardia with variable intensity of the heart sounds. There were no murmurs. The lungs revealed expiratory and inspiratory wheezes with scattered rales and rhonchi. The abdominal examination revealed tenderness in the right upper quadrant but no palpable liver or spleen. Distal pulses were present and the extremities were not cold.

A blood count revealed a hemoglobin of 13.3 gm. per cent with a white cell count of 11,500 per cu. mm. and 64 per cent neutrophils. The sputum smear showed predominantly gram-positive diplococci although the cultures of both sputum and blood were later reported as showing no growth. The x-ray film of the chest obtained on admission demonstrated poorly defined, almost homogeneous densities in the right lung field with similar lesser densities in the left lung field. The heart was slightly enlarged but exact evaluation was not possible in the single film because of moderate scoliosis. Pulmonary vascular shadows were increased. The appearance suggested pulmonary edema or bronchopneumonia more marked on the right side. The electrocardiogram obtained on admission is shown in Figure 1.

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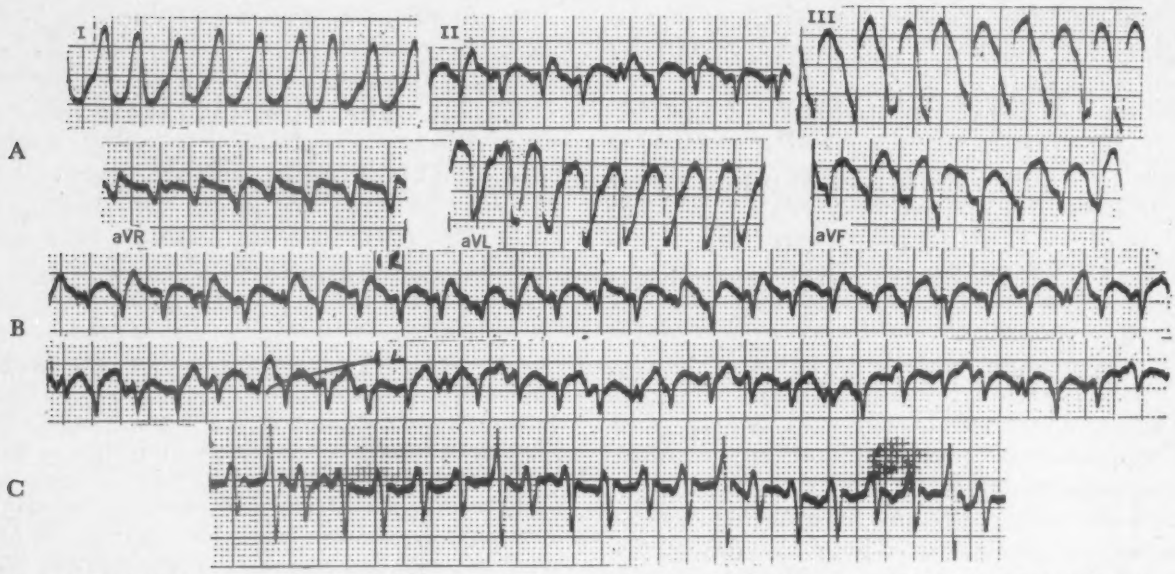

FIG. 1. A, the limb leads show a tachycardia and the configuration of left bundle branch block. B, the ineffectiveness of carotid sinus pressure is demonstrated. Upper strip, right side. Lower strip, left side. C, Lead V_2 shows a probable fusion beat at every sixth QRS complex. The rhythm is slightly irregular and there is evidence of independent atrial rhythm; rate 215 per minute.

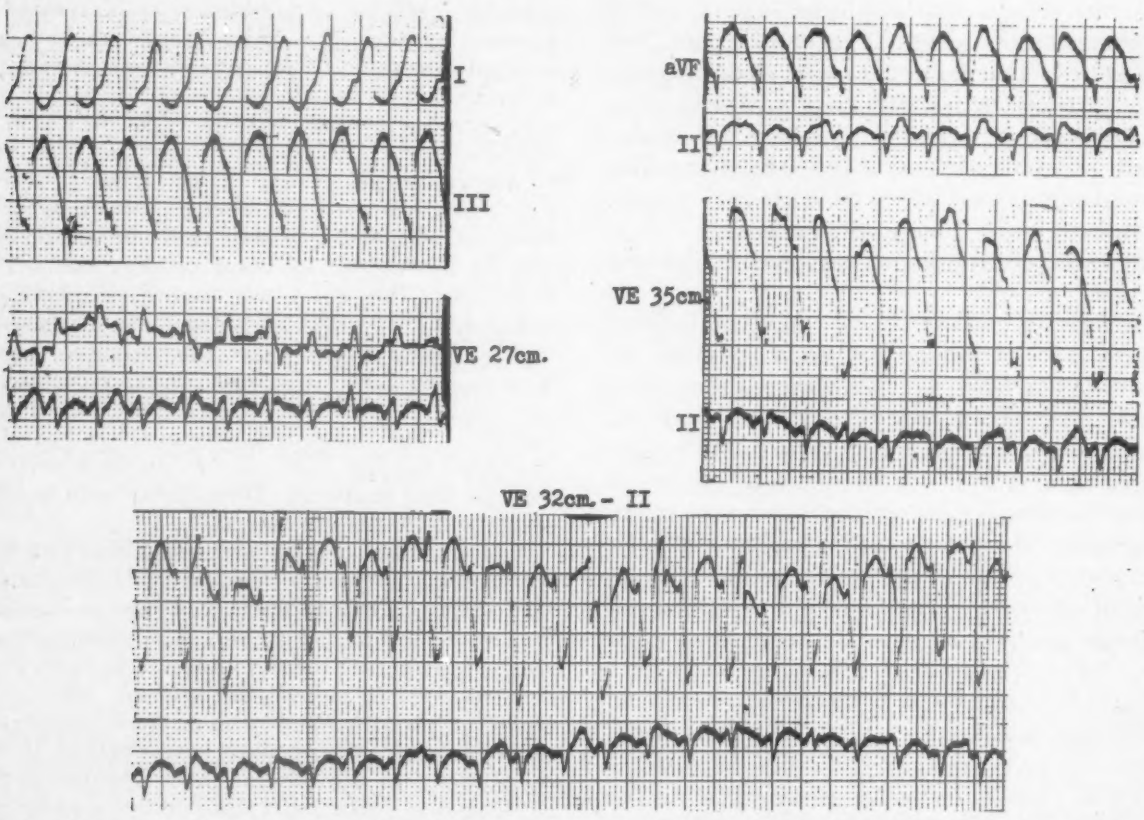

FIG. 2. Esophageal leads at various levels and simultaneous limb leads. An independent atrial rhythm at a rate of 110 per minute with a ventricular rate of 214 per minute is clearly seen at the 27 and 32 cm. levels.

Treatment was begun in the accident ward with nasal oxygen and, on the basis of an electrocardiographic interpretation of supraventricular tachycardia with aberration, deslanoside was administered intravenously in an initial dose of 0.8 mg. Following transfer to the ward, the patient's clinical condition remained stable; no evidence of shock developed. Penicillin therapy was initiated. Carotid sinus

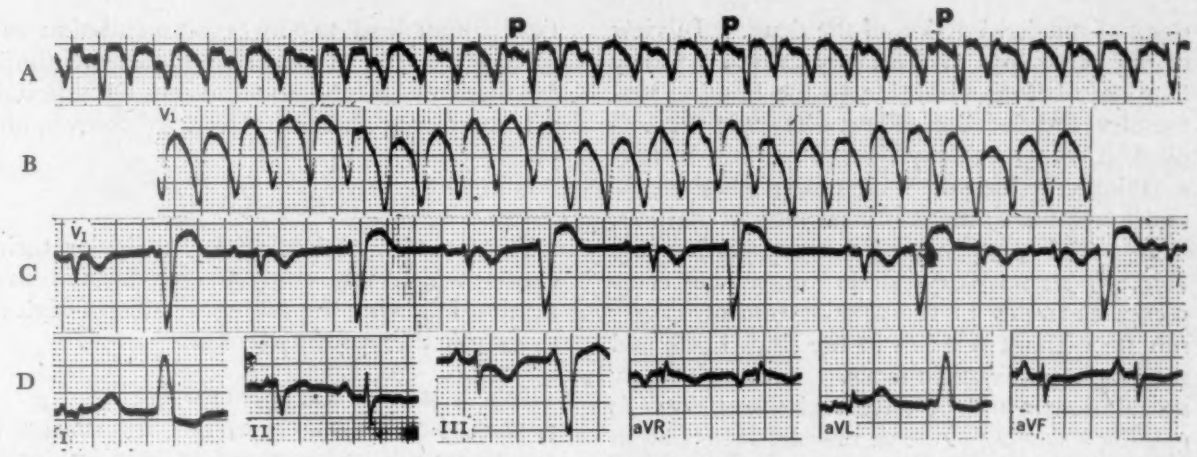

FIG. 3. A, lead II shows fusion beats at every sixth QRS. Careful observation and comparison with the esophageal leads in Figure 2 demonstrates a P wave before each fusion complex. B and C, lead V_1 before and after conversion. Note the similarity of the ventricular extrasystolic complexes after conversion to the complexes of the arrhythmia. This is also seen in the limb leads (D). Note that the extrasystolic ventricular rate in V_1 after conversion is 43 per minute and the complexes are not related to the sinus beats.

pressure was applied several times without producing any change in the rate or the rhythm (Fig. 1). The intravenous deslanoside was continued in a dose of 0.4 mg. at two hour intervals. Approximately five hours after the initiation of digitalis therapy an esophageal electrode was passed and the tracings shown in Figure 2 were obtained. Carotid sinus pressure was applied while the electrode was in place, again with no response, and the electrode was withdrawn.

Several minutes later, the patient commented that his heart rate had slowed. His pulse was 92 per minute and irregular, blood pressure 110/70 mm. Hg and temperature 101.8°F. The electrocardiograms in Figure 3 were obtained. He had received a total of 1.6 mg. of deslanoside within five hours; the last dose one hour before the change in rate. In view of the response, the patient was then given digitalis leaf orally and no other cardiac drugs were administered.

Blood electrolyte values obtained soon after admission and prior to conversion were as follows: carbon dioxide, 17 mM; chloride 94 mEq./L.; sodium, 132 mEq./L. and potassium, 4.1 mEq./L. The sugar and blood urea nitrogen were within normal limits. The serum glutamic oxalacetic transaminase was 28.5 units. Serologic reaction for syphilis was positive.

The fever and findings in the chest previously mentioned responded slowly to penicillin therapy over several days. There was no abrupt change in the chest. Repeat x-ray findings of the chest three days later confirmed nearly complete clearing of the densities in the lung fields. The heart appeared smaller in size.

On discharge he was given digitalis leaf, 100 mg. daily. He has been maintained on this drug during the past two and a half years without evidence of recurrence of the arrhythmia or heart failure.

COMMENTS

This patient was admitted with a rapid rhythm. The rate of 210 per minute although rapid for ventricular tachycardia is within the reported range.[5] The criteria for ventricular tachycardia[6] are fulfilled by the electrocardiograms of this patient, namely: ventricular beats of bizarre contour with a prolonged QRS duration of more than 0.12 second and the T wave opposite in direction to and continuing from the QRS complex, P waves identified at an independent and slower rate, occasional conducted beats with the QRS complex less prolonged than the beats of the tachycardia and the presence of ventricular fusion beats with configuration between ectopic and sinus impulses with no subsequent evidence of the pre-excitation syndrome. The QRS complexes are bizarre and have the configuration of left bundle branch block. The presence of fusion beats which appear to occur at appropriate intervals in relation to atrial beats is demonstrated. Sinus capture beats are not seen in the available electrocardiograms, possibly because of the rapid ventricular rate. Extrasystolic ventricular beats occurring after conversion to sinus rhythm resemble the complexes of the tachycardia. The diagnosis of ventricular tachycardia seems definite.

The only therapeutic agent this patient received was digitalis. No other cardiac drug was administered or has been found necessary since cessation of the rapid rhythm. The temporal relationship, the cessation of the tachycardia one hour following the last intravenous dose of deslanoside, corresponds to that expected for the

onset of maximal action of the drug.[7] In view of the persistence of the tachycardia for nearly four days before admission to the hospital and the observed duration of seven hours in the hospital, it seems unlikely that conversion to normal sinus rhythm would have been spontaneous and unrelated to the administration of digitalis. The initial postconversion electrocardiogram (Fig. 3) shows extrasystolic ventricular complexes occurring at the regular rate of 43 per minute without relation to the sinus beats and suggests a parasystolic focus. Although many speculations could be advanced about digitalis causing a slowing of the ventricular focus until a sinus mechanism could resume control these are not justified on the basis of a single case. Conversion of the ventricular tachycardia by digitalis in this patient appears most probable.

Previous reports of digitalis therapy in the treatment of ventricular tachycardia have been scanty and were recently summarized.[1] The principal objection to the use of digitalis seems to be the frequency of ventricular arrhythmias with toxic doses of the drug. This objection might also apply to quinidine or procaine amide.[7] Suggestions have recently been made that digitalis should not be withheld in ventricular tachycardia if failure supervenes.[8] This unique case demonstrates the ability of digitalis alone to convert ventricular tachycardia to normal sinus rhythm. This single observation cannot lead to any recommendation concerning the use of digitalis in this arrythmia. Further cautious therapeutic trials with digitalis are necessary before rejecting conventional prohibitions.

Summary

A case of a patient with ventricular tachycardia which was converted to normal sinus rhythm following the administration of digitalis as the sole therapeutic agent is reported.

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Intractable Ventricular Tachycardia

Unusual Mode of Conversion to Normal Rhythm Following Intravenous Procaine Amide*

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THE FOLLOWING CASE of prolonged ventricular tachycardia is of interest because of the large dose of intravenous procaine amide required for conversion to normal rhythm. The procedure was suggested by a recent report by Embree and Levine;[1] however, the technic employed was somewhat different. The unusual mode of conversion noted in the electrocardiograms was also of interest.

CASE REPORT

The patient, a white man aged thirty-seven, was first admitted to Holy Cross Hospital on February 15, 1959 because of retrosternal pain and pain in the left arm of fifteen minutes' duration. Serial electrocardiograms showed signs of acute anterolateral subendocardial ischemia which disappeared in one week. The patient was treated with the anticoagulant phenprocumon (Liquamar®) and was discharged on February 28.

He was readmitted the following morning, March 1, 1959, because of collapse and severe pain in the chest. Serial electrocardiograms were indicative of a massive anteroseptal and anterolateral infarction. SGO-T and erythrocyte sedimentation rate rose to abnormal levels. The hospital course was uneventful and the patient was discharged on March 20, 1959. Anticoagulant therapy was continued following discharge.

Initial Attacks of Paroxysmal Tachycardia: The patient's course was without incident until May 2, 1959, when he was readmitted because of crushing pain in the chest, nausea, blood-tinged vomitus and palpitations. An electrocardiogram revealed ventricular tachycardia, rate 190, apparently originating from a left ventricular focus (Fig. 1A). This readily reverted to normal sinus rhythm after administration of four doses of 250 mg. of procaine amide (Pronestyl®) intramuscularly at two-hour intervals.

Serial electrocardiograms after conversion did not reveal fresh infarction. SGO-T levels were elevated to 148 units during the first three days of hospitalization but the erythrocyte sedimentation rate remained within normal limits. His course was further complicated by an initial prothrombin time of 80 seconds and evidence of loss of blood (hematocrit 32 per cent and hemoglobin 9.7 gm. per 100 ml.). The elevated prothrombin time was readily returned to therapeutic levels with vitamin K_1 (Mephyton®). One unit of whole blood was administered to replace the blood lost and to avoid coronary artery insufficiency secondary to the anemia. An upper gastrointestinal series failed to reveal any abnormality. The patient was maintained on phenprocumon and quinidine sulfate, 0.6 gm. orally daily during his hospital stay and discharged on this dosage on May 15, 1959.

The patient was able to carry on his usual activities until July 15, 1959 when he was readmitted to the hospital with another attack of ventricular tachycardia arising from a similar left ventricular focus. This was readily converted to normal sinus rhythm by the addition of 0.6 gm. of quinidine sulfate to the maintenance dose over a two-hour period. He was discharged on July 17, 1959. His course was subsequently uneventful except for brief episodes of palpitation which the patient would control by taking an additional 0.2 gm. of quinidine sulfate orally.

Numerous electrocardiograms were obtained subsequently; results were essentially the same as those on February 21, 1960 (Fig. 1B) indicative of a previous anteroseptal infarct with probable anterolateral extension and ventricular aneurysm.

Persistent Ventricular Tachycardia: On February 18, 1960 he sustained another bout of persistent rapid heart action (Fig. 1C). This abnormal rhythm differed from the previous ones. Normal atrial activity was evidenced by the upright P waves in lead II at a rate of 102 per minute. The ventricular rate was 126 per minute and the ventricular complexes revealed an aberrant form as seen in ventricular tachycardia. There was complete atrioventricular dissociation. This might also be interpreted as an A-V nodal rhythm with intraventricular block and independent atrial rhythm. Nevertheless, the rhythm was considered to be ventricular tachycardia with a high ventricular focus.

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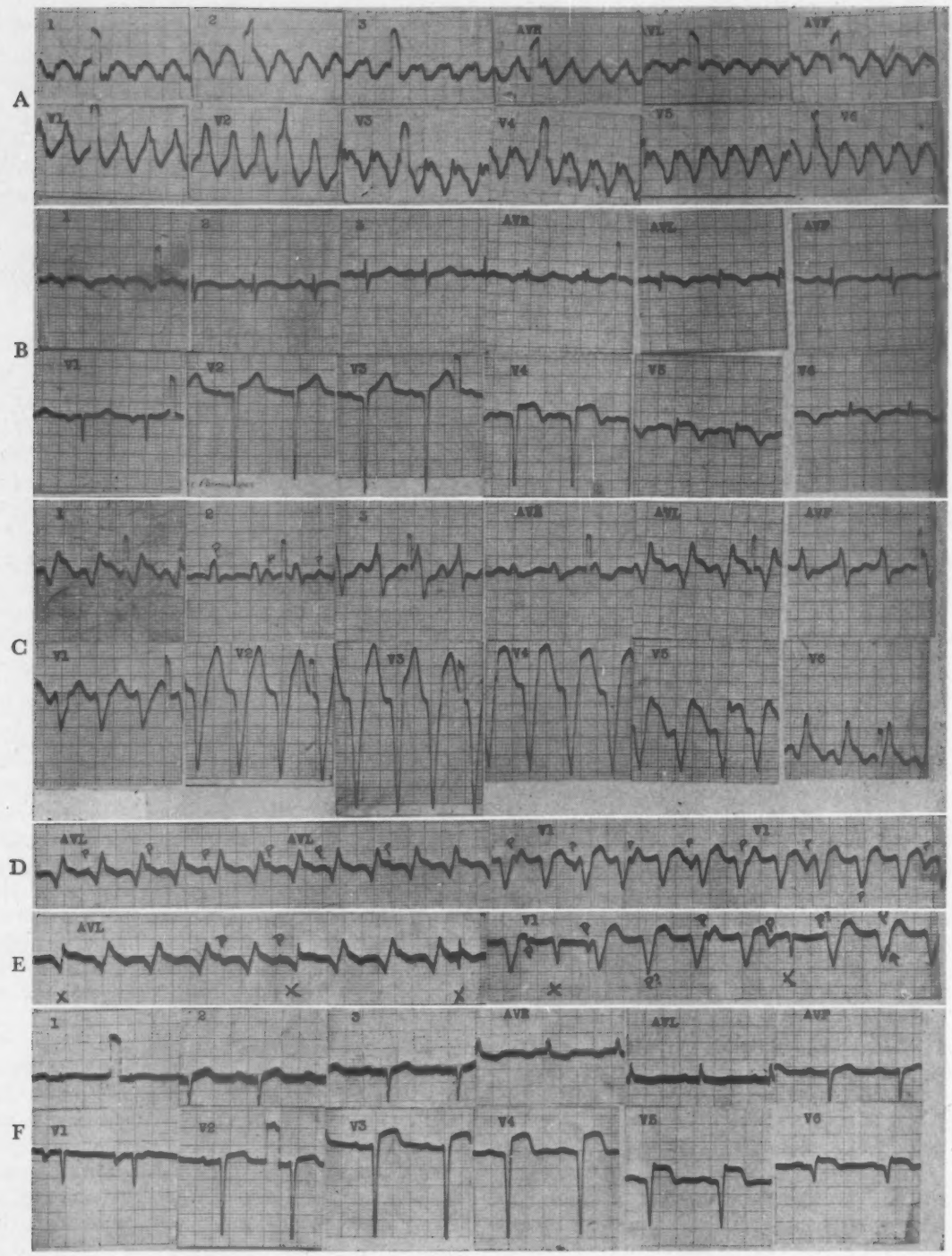

FIG. 1. Serial electrocardiograms. A, obtained May 2, 1959. Ventricular tachycardia with focus in left ventricle. B, obtained February 12, 1960. Normal sinus rhythm with signs of previous anteroseptal and anterolateral myocardial infarction. C, obtained February 18, 1960. Paroxysmal ventricular tachycardia with high ventricular focus. D, obtained March 16, 1960, at onset of intravenous infusion of procaine amide. E, obtained March 16, 1960, after infusion of 2,000 mg. procaine amide. F, obtained March 16, 1960, after conversion to sinus rhythm with 3,940 mg. procaine amide intravenously.

Auscultation revealed changing intensity of the first heart sound in the presence of a regular rhythm, confirming the electrocardiographic impression of A-V dissociation. Carotid sinus pressure caused no change in rate.

The patient received various combinations of oral gitalin (Gitaligin®), oral hydroxyzine pamoate (Vistaril®), oral and intramuscular procaine amide and oral quinidine sulfate and gluconate as indicated in Figure 2. He also received 4 gm. of oral potassium

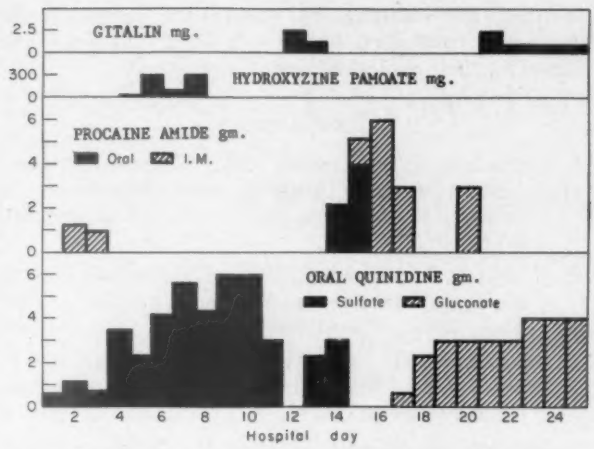

FIG. 2. Amounts and mode of administration of antiarrhythmic drugs administered over a twenty-five day period prior to intravenous infusion of procaine amide.

chloride daily. The atrial rate would slow to 77 per minute and the ventricular rate to as low as 112 but the basic pattern remained the same. At one time the P waves were replaced by atrial fibrillary waves with the regular rhythm of the ventricles being unaltered. On March 10, 1960 dyspnea, sacral and pedal edema, hepatomegaly and cardiomegaly appeared which did not respond to gitalin and hydrochlorothiazide. Despite the persistent tachycardia there was no pain in the chest and the erythrocyte sedimentation rate, SGO-T and white blood count remained within normal limits. Nevertheless, the patient's general condition deteriorated rapidly because of congestive failure.

It was decided to use procaine amide intravenously. Because of the resistance to oral and intramuscular administration, it was believed that a large dose intravenously would be required if conversion were to occur. The congestive failure, severe myocardial damage and the A-V dissociation were considered predisposing factors for ventricular fibrillation or standstill. Therefore, the patient was taken to the operating room so that facilities for a thoracotomy, defibrillation and cardiac massage would be immediately available if needed. A surgeon and an anesthesiologist were present. Procaine amide, 4 gm., was diluted in 400 cc. of 5 per cent glucose in distilled water, resulting in a solution containing 1 mg. per drop. The infusion was started at a rate of 40 drops per minute and gradually increased to 68 drops per minute. A total of 3,940 mg. of procaine amide was administered over a period of eighty minutes when conversion to sinus rhythm occurred. The infusion was promptly stopped.

The change in rhythm and conduction preceding conversion was unusual. At the onset (Fig. 1D) the atrial rate was 88 per minute and the ventricular rate 130. The QRS duration was about 0.16 second. After 2000 mg. of procaine amide had been administered the atrial rate was 85 per minute and the ventricular rate was 110 (Fig. 1E). There was insignificant widening of the QRS. Complexes of sinus origin giving rise to near normal ventricular activation began to occur. There was a gradual maximal slowing of the atrial rate to 74 per minute and the ventricular rate to 94, with persistence of the occasional supraventricular complexes. Conversion to sinus rhythm (with slightly delayed atrioventricular conduction) then occurred at rate 73 (Fig. 1F). The increased elevation of S-T segment was due to a "post-tachycardial syndrome" inasmuch as the electrocardiogram reverted to a pattern similar to that in Figure 1B within a week.

During the procedure the initial blood pressure was 92/60 mm. Hg and rose spontaneously to 110/70 when the infusion was started. Methoxamine (Vasoxyl®), 10 mg., was added to the infusion sixty-five minutes after start of administration because the blood pressure dropped to 76/52 mm. Hg. Ten minutes later it dropped further to 70/50 mm. Hg and an additional dose of 20 mg. of methoxamine was injected intravenously. After conversion, the blood pressure rose to 90/70 mm. Hg and stabilized an hour later at 110-100/70-50. After fifty-five minutes of infusion, 0.8 mg. of atropine sulfate was given intravenously without effect on the rate which had slowed to 104 per minute.

The therapy had no significant neurologic effect. Throughout the procedure the patient was conscious and rational. He experienced no subjective sensations when conversion occurred. The only obvious neurologic finding was a tremor of the lower jaw which persisted throughout the infusion. This was probably a reaction on an emotional basis and not due to procaine amide toxicity.

COMMENTS

Although the dose of procaine amide required for conversion was not without precedent,[1] the amount was large. The toxicity of the drug is well known.[2] The use of the drug intravenously warrants precautions against ventricular fibrillation, cardiac and respiratory arrest. Since time is the essential factor in preventing death or a vegetative existence from these catastrophes, precautions of the nature indicated in the protocol were taken. A surgeon and an anesthesiologist stood by with adequate ancillary help.

The mode of conversion was unusual in that it was not abrupt as is generally considered.[3,4] After 2,000 mg. of procaine amide had been given intravenously, complexes of sinus origin strikingly similar to those after conversion began to appear and persisted until conversion. Unfortunately, no record was obtained at the exact moment the event occurred. The physiologic mode of action of the drug is uncertain. Cer-

tainly, it apparently did not depress conductivity through the A-V node and the bundle of His.[2]

At present, the patient is alive and well, being maintained with 2 gm. of quinidine gluconate daily and anticoagulant therapy.

Summary

A case of paroxysmal ventricular tachycardia of twenty-eight days' duration failed to respond to large doses of oral and intramuscular antiarrhythmic drugs. Conversion was accomplished following the administration of 3,940 mg. of procaine amide intravenously in eighty minutes.

Acknowledgment

I wish to thank Drs. Bert Marks and Edward J. Zabinski and the operating room staff at Holy Cross Hospital for standing by during the procedure of conversion, and Drs. Richard J. Bing and John W. Keyes for their clinical advice.

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Persistent Ventricular Tachycardia

Report of a Case Successfully Treated with Very Large Intravenous Doses of Procaine Amide*

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Ventricular tachycardia is a relatively uncommon form of ectopic rhythm noted predominantly in patients with severe heart disease,[1] although it may occasionally be precipitated by excessive doses of digitalis and, rarely, it occurs in otherwise healthy persons.[1,2] The onset is abrupt, the heart rate is usually extremely rapid, the circulation is impaired and the blood pressure falls. Because this disorder usually occurs in patients with badly damaged hearts who are unable to withstand the added burden of rapid heart action and reduced blood flow, treatment often presents the urgent problem of how to correct the tachycardia before intractable cardiac failure, ventricular fibrillation and death ensue.[1-3]

The present report concerns a severe case of ventricular tachycardia which required heroic therapeutic measures for control. The patient finally responded to treatment after procaine amide (Pronestyl®) had been added to the regimen in extraordinarily large doses; the drug was administered in what may be the highest intravenous doses yet employed in the treatment of cardiac arrhythmias. Embree and Levine[2] have reported restoration of normal rhythm in a patient with ventricular tachycardia following the intravenous administration of up to 4 gm. procaine amide and 1 mg. atropine. In the present case intravenous doses of procaine amide ranged from 0.6 gm. to 4.8 gm. This case seems to us to be noteworthy because it illustrates the dramatic success that may attend vigorous and persistent therapy in an apparently hopeless case of ventricular tachycardia.

Case Report

The patient, a farmer and laborer forty-eight years of age, had been in apparent good health until March 24, 1958 when substernal pain associated with exertional dyspnea developed. These symptoms subsided spontaneously but continued to recur at frequent intervals with increasing severity until the patient sought medical aid. He was first admitted to the North Adams Hospital for treatment on March 31, 1958.

Examination on admission revealed that the patient was acutely ill; pulse rate 100 per minute, respiration 32 per minute and blood pressure 100/80 mm. Hg. An electrocardiogram the next day demonstrated changes typical of acute inferior wall infarction. Laboratory studies disclosed a white blood count of 15,200 per cu. mm. and an erythrocyte sedimentation rate of 33 mm. The patient was given complete bed rest. Digitalis therapy and other appropriate measures were initiated.

Initial Treatment of Ventricular Tachycardia: On April 6, the seventh day in the hospital, the patient became apprehensive, dyspneic and orthopneic. His radial pulse was 120 per minute and blood pressure was 90/56 mm. Hg. There were signs of left-sided cardiac failure. On April 7 the apical heart rate was 220 per minute and the blood pressure was 80/0. An electrocardiogram (Fig. 1A) showed a typical pattern of ventricular tachycardia. Therapy was immediately initiated and the various measures employed for the succeeding twelve days before restoration of normal rhythm in this patient are summarized in Table I.

The digitalis administered prior to the onset of the tachycardia was continued throughout subsequent treatment. On April 7, quinidine was prescribed and was continued in increasing doses for the succeeding forty-eight hours, both by mouth (2 gm.) and by intramuscular administration (2.6 gm.). The QRS interval widened from 0.12 to 0.16 second (Fig. 1B) and the apical rate fell from 220

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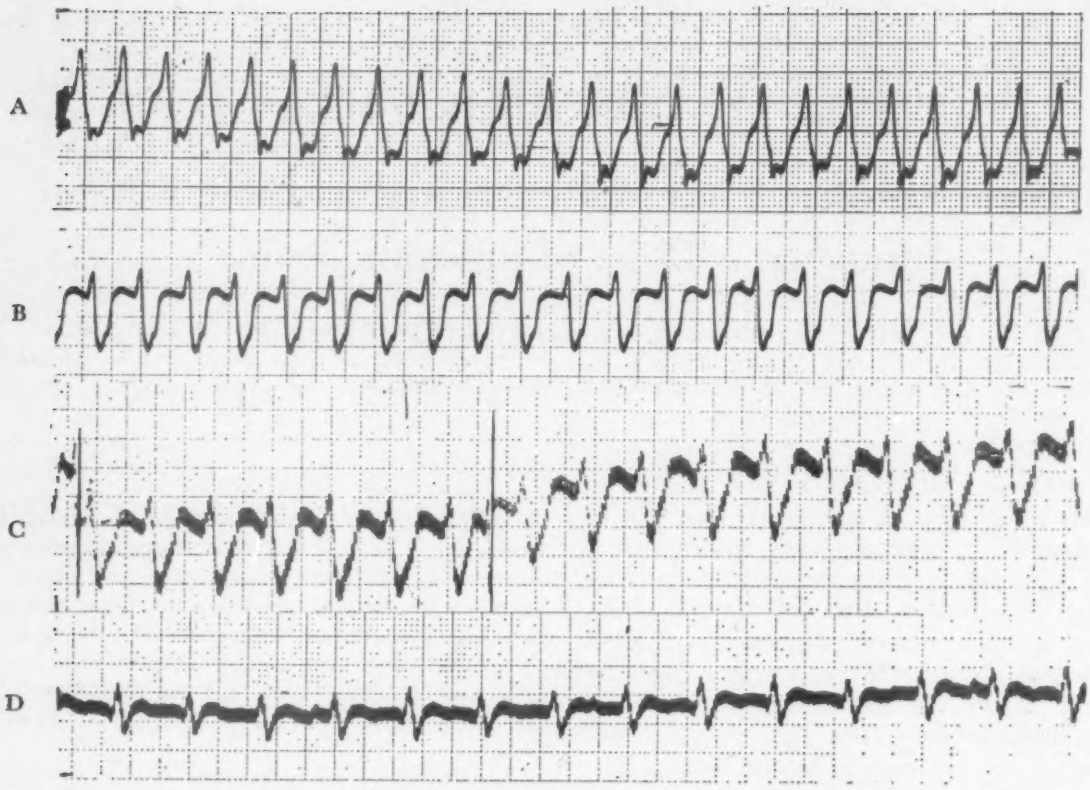

FIG. 1. A, April 7th, lead V_4. Ventricular tachycardia, rate 200. Before treatment. B, April 9th, lead II. After quinidine orally and intramuscularly. QRS measures 0.16 second. C, April 9th, lead II. After administration of 2.5 gm. procaine amide intravenously. Before conversion. QRS measures 0.20 second. D, April 9th, lead II. Immediately after administration of 2.5 gm. procaine amide intravenously. Conversion to nodal rhythm, probably with A-V dissociation, rate 120.

to 172 per minute, but thereafter the tachycardia persisted with the heart rate becoming increasingly rapid. The patient exhibited mild symptoms of nausea and vomiting.

On April 9, with the patient's situation obviously becoming increasingly precarious, procaine amide was added to the regimen. Before treatment with this was started a cardiac pacemaker was attached to the patient and during the intravenous administration of the drug, continuous electrocardiographic tracings were recorded. Initially, 3 gm. of procaine amide in 30 cc. of diluent was given intravenously over a period of thirty minutes. After 2.5 gm. had been received, onset of nodal rhythm was observed (Fig. 1D), with a heart rate of 110 to 120 and a rise in blood pressure to 128/90. Before nodal rhythm began the QRS interval had widened from 0.16 to 0.2 second (Fig. 1C). Side effects had also appeared in the form of epigastric burning, nausea and one episode of vomiting. After these symptoms subsided, the patient showed a general clinical improvement. An electrocardiogram recorded twelve hours after conversion revealed normal sinus rhythm. The blood pressure was 100/70 mm. Hg.

Second Episode of Ventricular Tachycardia: Regular rhythm with frequent extrasystoles continued for the next few hours until 2:00 P.M. on April 10, when ventricular tachycardia suddenly recurred. The heart rate increased to 190 and the blood pressure declined to 84/78. The patient exhibited profuse perspiration with marked dyspnea and weakness. Again, large oral doses of quinidine and procaine amide were administered (Fig. 2A), followed some hours later by the intravenous infusion of 3 gm. of procaine amide in 30 cc. of diluent over a period of half an hour. Following this vigorous therapy the heart rate again slowed from 190 to 165 and finally to 130; the tachycardia persisted. On the following day the heart rate increased to 172. Procaine amide was administered intravenously again in a total dose of 4.8 gm. in thirty-five minutes. Irregular nodal rhythm appeared after 4 gm. of the drug had been received (Fig. 2B), and regular sinus rhythm was observed after the total dose of 4.8 gm. had been given (Fig. 2C, D).

Third Episode of Ventricular Tachycardia: For the next seven days (April 12 to 17), the patient was maintained with oral doses of procaine amide, quinidine and digitalis; the heart rate remained within a normal range. On April 18, convulsions suddenly developed and the patient became intensely cyanotic. Ventricular rate was 200 beats per minute. In this

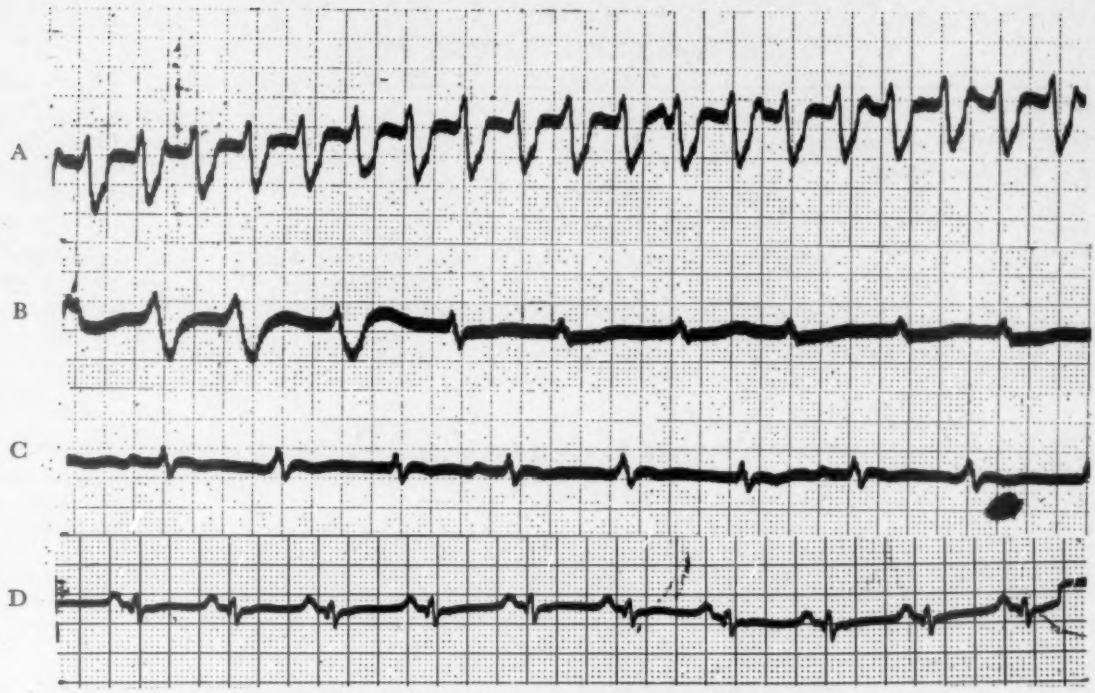

FIG. 2. A, April 11th, lead II. Ventricular tachycardia, rate 170. Patient receiving quinidine and procaine amide orally. B, April 11th, lead II. After administration of 4 gm. procaine amide intravenously. Conversion from slow ventricular tachycardia to nodal rhythm, rate 80. C, April 11th, lead II. After 4.8 gm. of procaine amide intravenously. Mixture of sinus and nodal rhythm. D, April 12th, lead III. Twelve hours after tracing C.

seemingly terminal situation, the immediate intravenous administration of 1 gm. of procaine amide in 10 cc. of diluent over a period of fifteen minutes once again was followed by the appearance of regular sinus rhythm with a heart rate of 88. At 6:30 A.M. of the following day (April 19) the ventricular rate again increased to 200 per minute, when 0.6 gm. of procaine amide administered intravenously was again followed by conversion of the heart rate in this patient to normal sinus rhythm. The tachycardia did not recur and on May 12 the patient was discharged to carry on at home with moderately restricted activity. At that time, maintenance dose of quinidine was stopped but oral procaine amide was continued as a prophylactic measure.

Follow-up Examinations: The patient was seen on October 24, 1959, more than a year after his first examination. At that time he had no complaints and was carrying on normal activities. His blood pressure was 120/80 mm. Hg, pulse 76 per minute, the chest was clear and the heart sounds were of good quality. The electrocardiogram showed merely the residual signs of inferior wall damage. The patient was again seen on October 22, 1960. He stated that he had been in excellent health and denied any pain in the chest or impairment of exercise tolerance even when performing heavy labor or farming. On physical examination the blood pressure was 120/85 mm. Hg; pulse 60 per minute and regular and the heart sounds were excellent with regular sinus rhythm There was no evidence of cardiac decompensation.

COMMENTS

The critical role of procaine amide in helping to control the aberrant heart rhythm and tachycardia in this patient seems clear from the findings as summarized in Table I. Repeatedly, the intravenous administration of large doses of the drug over a relatively brief period of time was followed by the desired effect. The tachycardia persisted without the use of the drug. Intravenous doses of procaine amide required to restore regular sinus rhythm in this patient could almost be "titrated" within a range of 2.5 to 4.8 gm. The supportive role of the other medications administered in providing synergistic effect (especially quinidine, norepinephrine, potassium chloride and digitalis) cannot be appraised with any degree of accuracy. In the report of Embree and Levine,[2] doubt was expressed that the ventricular rate could have been converted to normal sinus rhythm in their patient treated with intravenous procaine amide in doses up to 4 gm. without concomitant administration of atropine.

TABLE I

Clinical Course of Patient and Effects of Treatment

Date	Dosage of Procaine Amide	Other Medications		Effect on Ventricular Rate and Electrocardiogram	Effect on Blood Pressure (mm. Hg) and Other Clinical Observations
		Drug	Dosage		
April 7	None	Digoxin Quinidine sulfate Potassium chloride	1 mg. IM* 2.4 gm. PO† 1.3 gm. PO	Rate decreased from 220 to 194/min. QRS widened from 0.12 to 0.14 sec. (Fig. 1A, B).	Blood pressure fell from 90/56 to 80/0. Patient showed signs of left-sided failure (dyspnea and orthopnea). Nausea was present.
April 8	None	Digoxin Quinidine sulfate Quinidine gluconate Potassium chloride Chlorothiazide Norepinephrine	0.5 mg. IM 1.6 gm. PO 2.6 gm. IM (0.4 gm. every 2 hours) 1.3 gm. PO, 20 mEq. IV‡ 1 gm. PO 2 mg./500 cc. IV (continuous drip)	Rate fell to 172/min.	Blood pressure rose to 106/84. Signs of left-sided failure persisted.
April 9	3 gm. IV (in 30 cc. diluent in 30 minutes)	Strychnine Atropine sulfate Digoxin Norepinephrine Quinidine gluconate	1/30 gr. IM 1/70 gr. IM 0.25 mg. PO 2 mg./500 cc. IV (continuous drip) 6 gm. IM (0.4 gm. every 2 hours × 15)	Rate fell from 200 to 164/min. QRS increased from 0.14 to 0.16 sec. following administration of quinidine. QRS increased to 0.20 sec. after procaine amide had been given, before tachycardia reverted to nodal rhythm with a rate of 120 after 2.5 gm. of procaine amide had been received (Fig. 1C, D).	Blood pressure unchanged until onset of nodal rhythm after which it rose to 128/90. Symptoms of epigastric burning, nausea, vomiting, restlessness and sweating developed after procaine amide had been added to the regimen but these passed and the patient showed marked clinical improvement.
April 10	4.5 gm. PO (from 3:00 A.M. to 9:15 P.M.) 3 gm. IV (from 9:15 P.M. to 9:30 P.M.) Supply of procaine amide exhausted	Quinidine sulfate Digoxin Chlorothiazide Potassium chloride Norepinephrine	2.4 gm. PO 0.25 mg. PO 1 gm. PO 1.3 gm. PO Slow drip IV	Electrocardiogram 12 hours after conversion revealed regular sinus rhythm with frequent ventricular premature beats; at 2:00 P.M. ventricular tachycardia with rate of 190. After IV procaine amide, QRS widened from 0.14 to 0.18 sec. and rate fell from 165 to 130 and slow ventricular tachycardia persisted.	Patient showed less dyspnea and orthopnea. Blood pressure was 100/70. After tachycardia reappeared there was diaphoresis, marked dyspnea and weakness. Blood pressure was 84/78. After IV procaine amide patient became restless and exhibited profuse diaphoresis.

* IM = intramuscularly; † PO = orally; ‡ IV = intravenously.

TABLE 1 *Continued*
Clinical Course of Patient and Effects of Treatment

Date	Dosage of Procaine Amide	Other Medications		Effect on Ventricular Rate and Electrocardiogram	Effect on Blood Pressure (mm. Hg) and Other Clinical Observations
		Drug	Dosage		
April 11	4.8 gm. IV (from 8:40 to 9:15 P.M.)	Quinidine sulfate Digoxin Potassium chloride Chlorothiazide Norepinephrine	3.4 gm. PO (from 8:00 A.M. to 8:00 P.M.) 0.25 mg. PO 1.3 gm. PO 1 gm. PO Continuous drip IV	Rate rose to 172 (Fig. 2A) but irregular nodal rhythm began after 4 gm. of procaine amide had been administered IV (Fig. 2B) and regular rhythm with a heart rate of 80 began after 4.8 mg. of procaine amide had been administered (Fig. 2C).	The patient showed general clinical improvement after conversion.
April 12 to April 17	3 gm. PO	Quinidine sulfate Norepinephrine	1.6 gm. PO Slow drip IV (discontinued April 13)	Regular sinus rhythm, rate 68 to 80 (Fig. 2D).	Blood pressure averaged 105/80. Patient much improved. Signs of cardiac decompensation receded.
April 18	1 gm. IV (in 15 min.)	Quinidine sulfate	1.6 gm. PO	Electrocardiogram at 8:15 A.M.: ventricular tachycardia. Rate 200 fell to 78 after IV procaine amide.	8:00 A.M. Generalized convulsions, cyanosis, weakness, sweating.
April 19	3 gm. PO 0.6 gm. IV	Quinidine sulfate	2.4 gm. PO	6:30 A.M. rate 200 followed by restoration to regular sinus rhythm, rate 78, after IV procaine amide.	Weakness, sweating.

Procaine amide depresses myocardial sensitivity to electrical stimulation as well as the rate and degree of impulse conduction.[4] The characteristic effects of the drug on the electrocardiogram are widening of the QRS complex, prolongation of P-R and Q-T intervals, changes in T wave lengths and, finally, complete ventricular asystole.[4] All of these changes were noted in the present case, at times to an alarming degree. However, one of the chief effects anticipated from administration of the drug, namely, a fall in blood pressure, was not a significant problem, perhaps because of the simultaneous use of the intravenous pressor agent norepinephrine.

SUMMARY

A case of ventricular tachycardia secondary to myocardial infarction is described. The patient was successfully treated by the repeated intravenous administration of procaine amide in doses ranging from 2.5 to 4.8 gm. over short periods of time. In critical situations in which ventricular tachycardia threatens the survival of the patient large intravenous doses of this drug, two to four times that usually recommended, may prove to be life-saving.

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Diagnostic Shelf

Graphic Expression of the Palpatory and Auscultatory Signs of A-V Fistula*

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THIS SIXTY-FIVE YEAR OLD white man experienced a gunshot wound in the left popliteal region forty-eight years before admission to the hospital at the age of seventeen while serving in the Russian army. Following removal of the bullet the surgeon noted a large pulsating mass in the left popliteal region which had been present ever since. The patient was admitted to the hospital for evaluation and therapy for chronic leukemia, symptoms of which became apparent one year preceding admission with the onset of bilateral pitting edema, weakness, dyspnea and generalized malaise. At that time he was treated with digitalis and diuretics and received a low salt diet.

Physical Examination: The patient appeared pale and chronically ill but in no acute distress. The blood pressure was 130/80 mm. Hg, pulse 100 per minute and regular, respirations 20. There were prominent neck veins with small pulsations. Crepitant rales were present at both lung bases posteriorly with dullness to percussion at the left base.

The cardiac apical impulse was at the fifth left interspace at the midclavicular line. $A_2 > P_2$. No murmurs or cardiomegaly were present.

The abdomen was moderately distended. The liver was felt three fingerbreadths below the left costal margin; the spleen was palpated below the level of the umbilicus. There was severe bilateral pedal edema. A large pulsating mass measuring 3.5 by 3 cm. was felt in the left popliteal region. This mass presented a *palpable thrill* and a *loud bruit* with a systolic and a diastolic component.

Laboratory Data: Teleoroentgenogram revealed slight cardiomegaly with bilateral pulmonary congestion, left pleural effusion and patchy pneumonitis. Blood count revealed hemoglobin, 8.6 gm. per 100 ml. (54 per cent); hematocrit, 27 per cent; red blood cell count, 2.5 million per cu. mm.; white blood cell count, 52,000 per cu. mm.

Pulse and Sound Tracings: Simultaneous tracings of the pulsations and of the sound vibrations of the popliteal mass were recorded (Fig. 1). The pulse was recorded with a crystal microphone connected to the AC input of the electrocardiogram amplifier; the sounds were recorded with a standard microphone and a "stethoscopic" method. Both microphones were connected to a single funnel held by the hand over the popliteal fossa while the patient was in a prone position. The photographic recording was obtained by means of a Sanborn Twin-beam.

The pulse of the mass was a single, high wave with no dicrotic component. It is noteworthy that vibrations of a medium high frequency are regularly superimposed over the pulse. They are the graphic expression of the palpable *thrill*.

The sound vibrations consist of a *continuous machinery murmur* with vibrations of different frequencies and visible accentuation during the ex-

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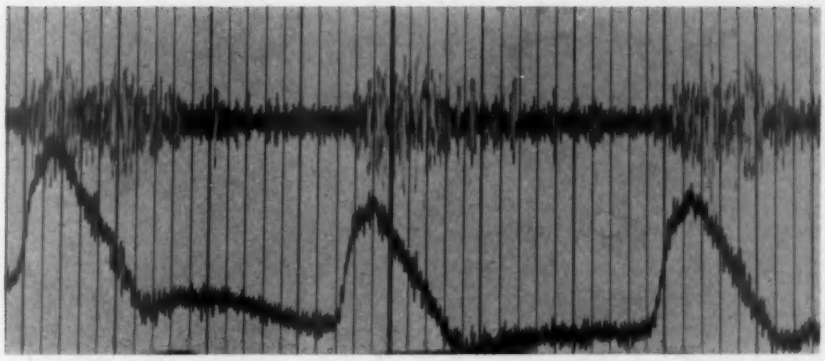

FIG. 1. Tracings at the left popliteal fossa over the pulsating mass. Top, sound tracing showing continuous murmurs. Bottom, pulse (revealing the thrill).

pansion and collapse of the artery. The murmur is similar to that of a patent ductus arteriosus.

Comment: The final diagnosis was *arteriovenous fistula of the popliteal vessels.* It is extremely unusual that an A-V fistula lasts forty-eight years without causing severe hemodynamic disturbances. It is unfortunate that the serious condition of the patient, caused by the leukemia, prevented further studies of his cardiovascular condition.

Progress Notes in Cardiology

Edited by EMANUEL GOLDBERGER, M.D., F.A.C.C.

New York, New York

Coincidence of Patent Ductus Arteriosus and Rheumatic Heart Disease: A Comment on the "Postcommissurotomy Syndrome"

THE FREQUENT OCCURRENCE of rheumatic heart disease in patients with atrial septal defects is now fairly well known. It is less well known that autopsy evidence of its association with many other congenital heart defects has been reported in several papers.

Drs. John A. Boone and Robert M. Rosemond have recently reviewed the records of seventy-three patients operated upon for patent ductus arteriosus at the heart clinic of the Medical College of South Carolina, Charleston, South Carolina. Thirty-six had adequate observation over a period of two to seven years following operation. Clinical evidence of rheumatic fever or a progressive valvular disease has appeared in six of the thirty-six patients. The study suggests a more frequent association between patent ductus arteriosus and rheumatic heart disease than has been previously suspected, and in some cases operation may have either precipitated or reactivated rheumatic fever.

They believe that these findings support the concept that the so-called "postcommissurotomy syndrome" following operations for mitral stenosis is a reactivation of rheumatic fever rather than a traumatic pericarditis. They further suggest long term observation following operations for congenital heart defects, particularly for the development of rheumatic heart disease, and that perhaps regular antibiotic prophylaxis should be instituted.

The Syndrome of Carotid Artery Insufficiency

IT IS BECOMING more apparent that partial or complete thrombosis of the internal carotid artery is the most common and important etiologic factor in producing cerebral vascular symptoms which hithertofore have been attributed to thrombosis of small blood vessels above the circle of Willis. This syndrome is of particular importance to physicians interested in cardiovascular disease because hypotension of any cause (but usually induced by myocardial infarction, hypotensive agents and postural hypotensive maneuvers) diminishes cerebral blood flow and induces cerebral vascular symptoms related to this obstruction. Drs. Lamar Crevasse, R. Bruce Logue and J. Willis Hurst (Department of Medicine, Emory University, Atlanta) have recently made a review of this syndrome (*Circulation*, 18: 924, 1958).

Recurrent episodes of transient motor or sensory symptoms are a frequent manifestation and may precede permanent neurologic deficits by months or years. Furthermore, more than half of these patients present aphasia and hemiplegia, closely simulating the "routine stroke." Careful palpation and auscultation of the carotid vessels should be done in all patients with cerebral vascular symptoms. Since the carotid bulb is the most common site of involvement, palpation of the neck and pharynx in instances of complete thrombosis may reveal an absent or markedly diminished pulsation. The results of direct arterial surgery in this group with complete thrombosis is dependent upon the duration of the thrombosis

and the ability to re-establish blood flow through the carotid; frequently the blood clot has extended higher into the head and neurologic symptoms have become irreversible.

Partial occlusion of the carotid is much more common than complete thrombosis and is expressed by the presence of a loud localized systolic or continuous murmur at this site. In one hundred consecutive patients in general hospitals, well-localized systolic murmurs occurred in seven and continuous murmurs were present in two. The majority of these patients were asymptomatic. Five to eight patients, however, with continuous murmurs over the carotid bulb had neurologic symptoms usually on the side opposite the carotid murmur. The continuous murmur is a new and valuable finding for insufficiency of the carotid artery. As the carotid lumen is narrowed by atheromatous deposits, a systolic murmur appears usually over the carotid bulb, the most common site of involvement. With further narrowing or when the collateral circulation becomes inadequate to maintain the diastolic pressure distal to the obstruction, turbulence of flow continues into diastole and produces a continuous murmur over a partially obstructed carotid bulb. These patients occasionally complain of a swishing or roaring in the head. Spontaneous falls in blood pressure or cardiac output usually associated with assuming the upright position may now produce transient neurologic symptoms opposite the side of carotid obstruction. When the vessel becomes completely occluded the murmurs disappear and subjective noises in the head cease. Irreversible deficits may follow, depending upon the adequacy of the collateral circulation.

The patients with this syndrome who most benefit from direct arterial surgery by endarterectomy are those with incomplete occlusions and transient symptoms of cerebral vascular insufficiency. Their neurologic examination is usually within normal limits and the only physical finding may be a localized systolic or continuous murmur over the partially occluded carotid bulb on the side opposite the neurologic symptoms.

Readings in Cardiology

From time to time, interesting books which ordinarily might escape the attention of cardiologists will be briefly reviewed in these columns.

Constrictive Pericarditis: "The chief disadvantage of the rigid constricting envelope in this disease is the limit it sets on ventricular filling in diastole. This puts an absolute ceiling on the stroke output of the heart. In most cases, both ventricles are constricted. Venous blood is dammed at a high pressure in the atriums and in the veins. Since the defect is not primarily in ventricular emptying, the early diastolic pressure of the ventricle is normal, but rises to the high atrial level very soon after the mitral and tricuspid valves open. The brief period of relatively normal pressure is called the "early diastolic dip." Although the combination of a marked dip and a virtually normal right ventricular systolic pressure is characteristic of constrictive pericarditis, it also occurs in other conditions interfering with normal diastolic filling. Occasionally, in severe cases, a markedly flattened right ventricular pressure is obtained. When the result of surgery is unsatisfactory, catheterization may help one to decide whether there is still constriction of the left ventricle.

"Similar catheterization findings have been reported in amyloidosis of the heart, subendocardial fibrosis, and the diffuse myocardial fibrosis that may complicate constrictive pericarditis. There is no adequate way by catheter study to distinguish these conditions from pericardial disease, which is the only one that can be helped by surgery."

The above quotation is from a very interesting book* which has just been published. In addition to a chapter on cardiac catheterization and other tests related to the cardiovascular system, there is an excellent chapter on pulmonary function tests which should be of interest to cardiologists. In addition, the full gamut of laboratory tests, including their significance, is presented.

* Syllabus of Laboratory Examinations in Clinical Diagnosis. Edited by Lot B. Page, M.D. and Perry J. Culver, M.D. Cambridge, 1960. Harvard University Press.

Workmen's Compensation for the Cardiac

Edited by Louis H. Sigler, M.D., F.A.C.C.

Brooklyn, New York

Case Discussions by Compensation Committee

In order to continue our studies on the important medical problems of causal relationship between physical and/or mental strain and cardiac disability and death, we shall present from time to time actual case reports for discussion by our committee members. We also invite noncommittee readers to discuss freely each case after its publication, giving reasons for refuting or affirming the various opinions expressed. These will be published in subsequent issues of the Journal. Please forward your discussion to the author's office at 255 Eastern Parkway, Brooklyn 38, New York.

For this month's discussion the following case from my files which is fairly typical of the usual run of compensation cases has been selected. The case is discussed by four members of our committee and I am adding my personal impression and attempt to correlate the views expressed.

Louis H. Sigler, M.D., F.A.C.C.
Chairman, Compensation Committee
American College of Cardiology

Myocardial Infarction Due to Physical Strain

Case Report

A Negro man, forty-three years of age, worked as garbage collector for the Sanitation Department for many years. His daily duties consisted of lifting heavy cans of garbage with the help of an assistant, each can weighing sixty to eighty pounds, into a truck which he drove from place to place. He was an obese, robust individual, exhibiting no symptoms at any time that might point to the possible presence of coronary disease. For the past two years, however, he did complain of "nervous indigestion." A gastrointestinal x-ray series showed no evidence of disease of the digestive tract.

One hot day he and his assistant did their usual work, loading one hundred cans of garbage into a truck in two and one-half hours. The total estimated amount of garbage was two and one-half tons. He apparently did not have any immediate subjective disturbances for he did not make any complaints. When he reached home, however, he told his wife that he felt hot and tired and he had "nervous indigestion" with cramping pain in the epigastrium. He had a light supper and retired early because of the pain. During the night he awoke several times. The next morning he returned to work and while in the garage changing his clothes he collapsed and died.

Autopsy: The heart weighed about 360 gm. The valves were normal. The aorta showed marked atherosclerosis and narrowing of both coronary ostia. The coronary arteries showed marked atherosclerosis and narrowing, especially the right coronary, which was congenitally small in addition to the narrowing. There was complete occlusion of the left circumflex branch by a small grayish thrombus beyond its junction with the anterior descending artery and there was also marked narrowing of the latter. The left main coronary artery before its branching had only a slitlike lumen caused by atheromatous deposits. There was an area of fresh softening of the

myocardium in the upper anterior wall of the left ventricle. The lungs showed congestion. The esophagus, stomach and duodenum were normal.

Committee Discussions

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The basic disease process is, in one respect, partly unrelated to occupation. Reference is here made to the congenital narrowing of the right coronary artery. The atheromatous stenosis of the coronary ostia probably is not occupational in origin either. However, it is not proved that the deceased workman had not been occupationally exposed to atherogenic agents. Garbage collectors are occasionally exposed to poisonous substances and this factor needs closer inquiry in this occupational group.

Next comes the *question of physical exertion* as a factor in the demise of this man. The exertion probably was not unusual for a garbage collector. Probably this man had done this type of work for years and had the muscular system and hemodynamic efficiency necessary to the task. Two questions, however, must be resolved: First, can repetitive hyperexertion slowly facilitate atheromatous degeneration of the coronary arteries? Second, assuming that a hypothetic end stage of progression of the atheromatous degeneration has been reached, can a single final hyperexertion under adverse climatic conditions lead to coronary occlusion and myocardial infarction?

Evidence That Exertion Was Not a Factor: Affirmative answers for either or both questions are likely to be strictly minority opinions. However, would a majority negative opinion have any truly factual basis other than (1) the statistical observation that large numbers of men perform arduous labor under adverse environmental conditions without coming to grief; (2) the information that regular performance of physical exertion is beneficial and may even correlate with a lesser prevalence of coronary atheromatosis; (3) the recorded occurrence of so-called silent coronary attacks in occupational groups; (4) the fact that disease of the coronary artery occurs in workers as well as nonworkers; (5) the truism that most coronary occlusions have their onset while the person is resting or occupied in some trivial exertion; and (6) myocardial infarction is relatively rare in Negroes in Africa where large numbers of men are arduously employed, often under very adverse climatic conditions.

Evidence That Exertion Was a Factor: These statistics, which are of course indisputable, do not, however, negate the possibility of exceptions to the rule. There are the following points to consider, all of which are subscribed to by the very same authorities who most strongly emphasize that exercise is good for everyone.

First, why do we exclude from arduous labor persons who have evidence of coronary insufficiency? Are there any physicians who will knowingly sign on such men for work? In most industries specific attention is given to cardiac health and all persons with indications of heart disease are either rejected or assigned to nonarduous activity. Second, we all are aware of the electrocardiographic changes which may occur after a Master's two step test and we all know how sensitive a person with coronary insufficiency is to oxygen deprivation. Third, we are all aware of the need for absolute rest in saving a life which has been jeopardized by coronary occlusion. Can we reconcile these facts with the opinion that physical exertion, particularly if arduous, can never induce myocardial infarction? In the present case, it seems to have been a factor in hastening the end.

One could become technical and discuss such matters as the effect of a hot humid environment versus a cool, dry working area in adding to the cardiac burden. One could also speculate about probable pathogenic events such as subendothelial hemorrhages, sludging and platelet deposition over atheromatous plaques. Will these considerations outweigh the statistics?

ERNST JOKL, M.D., F.A.C.C.
LEXINGTON, KENTUCKY

The forty-three year old patient was obese. Atheromatous deposits were present in the coronary arteries with narrowing as well as sclerosis, findings which reveal the chronic nature of the degenerative changes. Over the years preceding the sudden fatal collapse there had been complaints of "nervous indigestion."

Two well understood extraneous cardiovascular stress factors were operative on the day of the patient's death. It was hot and on the day prior to the collapse the deceased had carried out exceptionally hard physical work, lifting one hundred cans of garbage into a truck in a period of two and one-half hours. The heat undoubtedly gave rise to a shift of blood from the body cavities into the cutaneous vascular bed, a physiologic mechanism of adap-

tation which is more readily and more extensively evoked in obese than in lean persons. During the lifting of the garbage cans the Valsalva effect manifested itself repeatedly and caused the inflow of venous blood into the thorax to be sharply reduced. Under normal circumstances, however, catastrophic sequelae will not occur though it is not unusual even in healthy subjects for temporary functional disturbances to make their appearance, e.g., giddiness or fainting. I have described the clinical physiology of this syndrome in detail in *Acta Medica Orientalia*, March 1946.

Physical Stress and Subintimal Hemorrhage: If severe physiologic stresses are imposed upon a diseased arterial system, the changed hemodynamic state so brought about can produce acute cardiac ischemia as well as critical alterations of the mechanical force equilibrium or intravascular pressure gradients, with the result that microscopic tears of the intima may occur. The latter calamity most commonly befalls the left circumflex branch of the coronary artery.

Thrombus formation in an atheromatous and calcified branch of the coronary artery need not immediately be accompanied by symptoms, though it may well do so. However, Nelson (*J. Path. Bact.*, 53: 105, 1941) as well as French and Dock (*J. A. M. A.*, 124: 1233, 1944) have pointed out that physical activity increases the risk of bleeding into a hypertrophied intima or into atheromatous and calcified plaques in coronary arteries and that such hemorrhages may expedite fatal collapse in persons thus affected. In the case herein discussed it is possible that the thrombus had already been present at the time the patient went to work on the day of his death and that the collapse was the result of a fresh subendothelial hemorrhage. Occasionally one can be sure of the sequence of events if postmortem capillary penetration into an organizing thrombus is in evidence. It appears likely that this man's final collapse was caused by a subendothelial hemorrhage. Several years ago I gave an account of a similar case in *Lancet*, November 18, 1944, in which that was found to be the mechanism of death. That middle aged men of forty-three and even younger may thus be stricken was described by Master, Dack and Jaffe (*Arch. Int. Med.*, 64: 767, 1939).

Exercise and the Cardiovascular System: The case we are discussing here is of general importance in interpreting cause and effect on the basic relationship of physiologic and pathogenic factors in situations of this nature, that is, in situations in which the impact of strenuous exercise is imposed upon a diseased cardiovascular system. The degree of stability of the underlying pathologic process in these cases determines the clinical outcome. Exercise and exposure to climatic temperature variants will never cause the death of a healthy individual. However, the issue is different when the physiologic adaptations in question involve vascular structures that lack normal elasticity and resilience. Not that such individuals will always come to grief even during strenuous exercise. Many observations of outstanding athletes with cardiovascular afflictions testify to the validity of this statement. Exercise and training have come to play such an important role in geriatrics and rehabilitation precisely because in the course of their development, pathologic processes often reach a "steady state" in which, temporarily at least, there is no difference between healthy subjects and those with cardiovascular disease with regard to the response to the muscular effort. In pathology the term "steady state" has its own meaning, which is not the same as that attached to the corresponding designation used in physiology. A "steady state" of a pathologic process is the decisive prerequisite for the justification of applying active exercise as a therapeutic procedure in clinical medicine. The physician must invariably consider the alternate possibility of critical instability factors being present. Among the latter, loss of normal elasticity and resilience of the coronary intima represents in this context probably the most single source of danger in cardiology. The underlying degenerative vascular changes need not be systemic in their distribution. They may be narrowly localized and therefore difficult to detect *in vivo*.

I. ROBERT FRANK, M.D., F.A.C.C.
BOSTON, MASSACHUSETTS

This case report is a typical example of the problems we face all the time in the Industrial Accident Boards all over the country and which, in many cases, are difficult to judge satisfactorily.

I am of the opinion that there was causal relationship in this case for the following reasons:

1. This obese person had been suffering from bouts of coronary insufficiency for a few years rather than of "nervous indigestion." This is based upon the fact that gastrointestinal disease was ruled out during life and at the postmortem

examination. It is also a well known fact that only gastrointestinal symptoms may occur in cardiovascular disease. Aside from this, severe atherosclerotic changes were found at postmortem which had obviously been present for a long time. There was also congenital narrowing of the right coronary artery and the coronary ostia were narrowed and sclerotic. These pathologic changes are certainly the basic causes of coronary insufficiency and were in my opinion the basis for his "nervous indigestion."

2. We have an obese man who had been doing hard laborious work for a number of years, then one hot day when he had done an unusual amount of hard work compared with what he usually did, he went home, fatigued, hot, unable to eat more than a light meal, and had several attacks of epigastric pain during the night, followed by his demise later the following morning before he had started working. I would consider this to have been the natural sequel of a coronary occlusion, following a few years of coronary insufficiency. The autopsy revealed a complete occlusion of the left circumflex artery by a grayish thrombus which was the final fatal episode. Grayish thrombi are somewhat older than the red fresh thrombi and this could signify that the occlusion was present long enough to cause the area of fresh softening in the left ventricular wall. It is my opinion, therefore, that the occlusion occurred while he was working.

3. Despite the fact we all recognize that atherosclerosis and atheromatosis are natural degenerative processes, due to factors as yet unknown, and that patients with these conditions can live for many years, acute pathologic changes do take place during which an atheromatous plaque may rupture, or hemorrhage may occur into a plaque which then expands and ruptures, or a thrombus may form on a plaque, any of which may occlude the coronary lumen. These changes may occur as the result of a sudden increase in blood pressure due to the work the deceased was doing on the hot day before his demise, with the resultant complete occlusion that followed. I also believe that the only reason he did not have more difficulty, considering the markedly advanced atherosclerosis as shown at autopsy, is that he had built up a good collateral circulation as a result of repeated myocardial ischemia in the past. The hotter the day, the more work must be accomplished by the heart in order to maintain circulation of the blood near the body surface so that excess heat can be given off through the skin. It has been shown in normal men that the heart rate while lying still in a room heated to 104°F. with a relative humidity of 90 per cent is increased by 40 per cent at the end of an hour and 70 per cent at the end of two hours above normal. In this case we have a person with heart disease in which strain could be a very definite contributing factor.

4. Physical strain increases aortic pressure and also the intracoronary pressure transiently and may produce acute changes in coronary vessels in cases in which marked atheromatosis exists as in this patient. Strain may stimulate the sympathetic nervous system producing tachycardia, arrhythmia and cardiac overactivity, making greater demands on the coronary blood supply, and also producing general vasoconstriction with a rise in pressure transmitted to the coronary system. I believe, therefore, that the work was a cause of his death.

RONALD L. HAMILTON, M.D., F.A.C.C.
BINGHAMTON, NEW YORK

As I understand it, this man was an obese, robust person who had complained for two years of "nervous indigestion" and that during this time gastrointestinal x-ray studies showed no evidence of disease of the digestive tract. I do not understand the term "nervous indigestion" and the only clue we have is that it might have been due to coronary insufficiency. Unfortunately, the history does not state whether or not unusual effort or emotional disturbances made the "nervous indigestion" worse.

This man had advanced long standing atherosclerosis of his coronary arteries and certainly this was not produced by work. The man died, apparently, as the result of a fresh myocardial infarction and coronary thrombosis. In view of this diagnosis, I do not believe that the work done by this man in any way directly or indirectly contributed to his sudden death. It is a recognized fact coronary occlusion with myocardial infarction develops in 60 per cent of men during working hours and not because of work. The myocardial infarction occurred the day before the man died, evidenced by such remarks as "he ate a light supper, he retired early to bed because of epigastric pain and that he was awakened several times in the night."

LOUIS H. SIGLER, M.D., F.A.C.C. (CLOSING)

A factor of great importance in this case from a medicolegal viewpoint is that the claimant died suddenly while changing his clothes and before starting his usual strenuous physical work. One may therefore argue that the effort of changing his clothes was certainly not of sufficient severity to cause his death and therefore there was no causal relationship between the work he had done at that time and his death. We would have no definite ground to argue that the work done the previous day was the cause of his death the day after except for the statement by his wife that he had some symptoms the night before. Had there been no autopsy obtained in this case this testimony alone would have no great value. Indeed, many a claimant has probably lost his deserving compensation in the past under such circumstances. The autopsy findings in this case, however, demonstrated the presence of acute myocardial infarction which should have taken at least twelve to twenty-four hours to develop. This brings the time of the acute onset of the process to the period when he was doing his strenuous work and a temporal relationship may therefore be considered established.

Physical Strain and Coronary Atherosclerosis: The main question in this case remains therefore whether or not the strenuous work he had done the day before was a competent, producing cause of the pathologic condition and therefore his death. It has always been my contention that strain of sufficient severity may be a cause not only of an acute myocardial insult but, if performed over a prolonged period of time, is also one of the underlying causes of atherogenesis, especially of the coronary arteries. That it is not the only cause and that it may be only a relatively minor factor in some cases is, of course, true. Nevertheless, it should be considered a cause. One does not necessarily have to expose himself to an atherogenic poison in connection with his work to develop the pathologic changes. Mere marked alterations in the hemodynamics of the circulation from time to time under strain may in some cases predispose the subject to the pathologic changes in the course of time. This appears to be true of some persons more than of others. It is particularly true in the later stages of atherosclerosis when the sensitivity of the vascular system and its reactivity to strain become progressively greater. I have discussed this factor in previous communications.

Physical Strain and Acute Coronary Changes: The individual reaction of a given person to strain would explain why relatively few have acute attacks under strain. It is the abnormal person's reaction to strain which makes him vulnerable to an attack as against a person who develops a physiologic adaptation that Dr. Jokl rightly describes as a "steady state." A person who is not in a "steady state" need not be exposed to unusual strain to get an acute attack of coronary insufficiency or of occlusion and the resulting myocardial ischemia, necrosis or gross infarction. Ordinary and customary work, if strenuous enough, may bring about such an attack.

Another element we must bear in mind besides the individual sensitivity and reaction is that an acute cardiac insult and the resulting death is based not alone on anatomicopathologic alterations but also on physiologic changes. Death itself, although almost always accompanied by structural alterations which are considered to be the causes, is really not entirely due to such alterations. We frequently find cases in which the pathologic structural changes are severe and yet life lingers on. Other cases may show relatively little or no structural disease on postmortem examination and still the patient died unexpectedly. In our case under consideration the cause of death was probably a sudden onset of ventricular fibrillation which is a physiologic process induced by the local cardiac disease. The fibrillation evidently was partly caused by his little activity on the morning of his death. Had the acute cardiac disease been recognized the day before and proper therapy used, he might have lived. Indeed, if his coronary disease had been recognized during the two years of its unusual symptomatic expression, had his occupation been changed to a milder type of work and his weight reduced under careful management, the final acute cardiac insult could have been forstalled probably indefinitely.

The statement by Dr. Schepers that statistics speak against causal relationship of strain and cardiac disability, but that there are possibilities of exception, is perfectly true. It has always been my belief that the individual case may even be the rule in certain conditions and the large statistics to the contrary may be the exception in the pathogenesis of a disease process. For instance, we all know that diabetes mellitus occurs in a relatively small number of people in relation to the general population,

and statistically it should be considered against the rule in its occurrence. Yet, it is the rule in individuals who have a predisposition to the disease.

Conclusion: Based on all the facts in the case under discussion, there is no doubt as to causal relationship between the strain to which the claimant had been exposed and the myocardial infarction and death. It is nevertheless good to have the dissenting opinion of Dr. Hamilton. Dissension is the best stimulant to proper thought.

Letters to the Editor

Occlusion of Terminal Aorta for Congestive Heart Failure*

Dear Dr. Wassersug:

This is a follow-up note on Mrs. D. H. whom you referred to me in 1953. The most remarkable feature of this woman's case has to do with my very special friend and colleague, George Meneely of Vanderbilt University Medical School in Nashville, Tenn. Dr. Meneely in a semi-facetious way chided me for not correcting people with very limited cardiac reserve and limited cardiac output. He contended that the "Meneely Operation for Cardiac Insufficiency" would take care of many people with limited reserve. I believe that Dr. Meneely is a man of substance, highly intelligent, imaginative and resourceful. If he has an operation that he believes is reasonable for patients with limited myocardial reserve, I would give serious thought to his operation before discarding it. In exactly this spirit, I hesitated at the conclusion of his statement, but then said, "Please tell me more about your operation, George." He then continued and pointed out that patients with really borderline congestive failure could not get around very much on their legs and in this twentieth century, overcivilized, push-button state the legs were all but atavistic. Under these circumstances he recommended that the surgeon amputate the patient's legs.

At this point I believed that my collaboration with my friend George Meneely had come to an end, at least on this project, and the conversation ended. Today I have reason to describe to you again the circumstances surrounding the surgery for D. H. and to send a copy of this note to George Meneely.

In October 1953 Mrs. D. H. came to me in cardiac failure and with mitral insufficiency in a terminal state. I explored her heart and she had minimal mitral stenosis and free mitral insufficiency. I pulled a large lucite baffle into the mitral orifice hoping that the mobile leaflets, contracted as they were shortened to the point of free insufficiency, would with the addition of the lucite substance become competent. As I did this, the regurgitant flow was obstructed, ventricular size contracted, the chamber of the left ventricle became smaller, and the annulus of the mitral orifice apparently reduced so much in size that the lucite spindle not only corrected all insufficiency but totally obstructed all forward flow. The heart went promptly into arrest. I tried to resuscitate the heart but could obtain no forward flow; therefore, I hastily cut the lucite baffle free of its moorings on the outside of the heart and let it embolize freely into the aorta. I knew that it was too large to enter the carotid arteries; therefore wherever it went I might recover it and she would be a salvageable patient.

After the lucite baffle was forced into the left ventricle and out into the aorta, it was possible to resuscitate Mrs. H.'s heart. She made an essentially uneventful recovery. At first she had very little right femoral circulation but a viable leg. In June 1954 Dr. Chilton Crane took an aortogram and found that she had total obstruction of the abdominal aorta at its bifurcation. He hypothesized that she had partially obstructed her right iliac and slowly thrombosed the remaining cross sectional area of the right iliac and cross section of the lower aorta. Thus, in stages we have performed the Meneely operation at a level higher than Dr. Meneely's fondest hope would have allowed.

Today (September 2, 1960), Mrs. H. was brought in because of pain incident to her scoliosis but not incident to her heart disease or obstructed aorta. She has no pulse in the femoral arteries or below. She walks on level ground well enough for social purposes but her husband carries her upstairs. She can walk downstairs without too much difficulty. She does have marked hepatomegaly but her lungs are clear. She has no ascites. She sleeps on a backrest, giving her the equivalent of a three-pillow orthopnea. It is necessary to maintain her with digitalis and hydrochlorothiazide.

There is no question in my mind that this patient with free mitral insufficiency has a

* Because of its great interest the Editor is bringing this correspondence to the attention of our readers.

clear heart very little larger than it was at the time of surgery and, with her limited output, could scarcely have survived these seven years unless her total body requirements had been shunted into essential areas and her legs partially sacrificed.

This fascinating case is being brought to the attention of George Meneely. I will be interested in his reactions.

DWIGHT E. HARKEN, M.D., F.A.C.C.
Boston, Massachusetts

Dear Editor:

I have had an opportunity of reading Dr. Harken's letter describing the adventitious "Meneely operation" on Mrs. D. H. I am immeasurably pleased to hear about her. I do want to correct one impression conveyed in his letter: I did not *advocate* amputating a cardiac patient's legs, instead I pointed out that it would be *logical* to do so.

Let me amplify and extend this remark. It has been known for a long time that there are two main hemodynamic disturbances in heart failure. As Stead has neatly phrased it, not only is there an insufficient amount of circulation but what cardiac output exists is maldistributed. The two hind limbs of *homo sapiens recens* were mainly designed for the purpose of running away from dinosaurs. This is an activity in which the average patient with congestive heart failure is nowadays not called upon to engage. From his (or in the case of Mrs. H., her) point of view the hind limbs are massive arteriovenous fistulas irrigated by thumb-sized arteries to no useful purpose. For various reasons, ranging from the purely esthetic to the obviously practical one of being able to walk into a surgeon's office, these vestiges are deserving of preservation even if on a limited budget of circulating blood.

Now it is evident that there is not very much seriously wrong with most victims of Leriche's syndrome. As a result of the slowly developing aortic obstruction at the bifurcation there is often intermittent claudication of the hip with fast walking and sometimes a toe or two may be lost but this is nothing to compare with the gravity of the housebound or bedridden circumstance of the waterlogged patient with congestive failure. What I *have* advocated is the induction of Leriche's syndrome in patients with cardiac failure who no longer had enough circulation to irrigate adequately both the hind limbs and kidneys. I intended to leave to the genius of my cardiac surgical colleagues how best to accomplish technically this obviously desirable effect. The hand of the Lord and Dwight Harkens' keen observation have served to accomplish it unintended. As Sir John Harrington remarked, some things if we do not do them ourselves will be done for us.

Some experimental work has been done, although not as the doers meant. The South American maneuver of ligating the inferior vena cava (Cossio) has been shown to ameliorate congestive heart failure. It does so not by preventing blood from coming out of the hind parts but by damming it back, so preventing arterial flow from going in and redirecting much needed arterial flow to the kidneys.

For a number of years, I have been urging my surgical colleagues to try occlusion of the terminal aorta in congestive failure for the reasons outlined but until now without success. I had even appealed to you in the past whether you would publish in the AMERICAN JOURNAL OF CARDIOLOGY a communication entitled "An Open Letter to an as Yet Unknown Surgical Colleague" which was to contain much of the matter given herein. Dr. Harken's spectacular Mrs. H. renders this literary effort unnecessary. He has cast his lucite upon the cardiovascular waters and it has returned an hundredfold.

GEORGE R. MENEELY, M.D., F.A.C.C.
Nashville, Tennessee

Book Reviews

Cardiology: An Encyclopedia of the Cardiovascular System, edited by Aldo A. Luisada. Blakiston Division, McGraw-Hill Book Company, Inc., New York, 1959. Vol. 1. Normal Heart and Vessels, pp. 554. Vol. 2. Methods, pp. 608. Vol. 3. Clinical Cardiology, pp. 754. Vol. 4. Clinical Cardiology: Therapy, pp. 893. (Total pp. 2,799.) $100.00.

The aim of the editor, as expressed in the preface of this encyclopedia, was to present all available knowledge of the heart and blood vessels in a systematic order and in looseleaf form to allow frequent revisions and supplements. In these four volumes (a fifth is yet to come) the editor has successfully accomplished this heroic task.

Volume 1, devoted to the development, structure and functions of the cardiovascular system, contains short chapters on the embryology and anatomy of the heart and its main arteries. These are followed by authoritative sections on the physiology of myocardial contraction and metabolism, the origin of the heart beat and the basic principles underlying the physiologic functions of the cardiovascular system including the electrocardiogram, heart sounds, cardiac output, arterial pulse, dynamics of the blood vessels and regulation of the circulation to the heart, brain, kidneys and lungs.

Volume 2 deals with various clinical methods of studying the cardiovascular system. The pulsations of the peripheral and central arteries, veins, liver and chest wall are discussed as well as the technical and clinical aspects of electricardiography, phonocardiography and ballistocardiography and various radiographic technics including angiocardiography. Cardiac and pulmonary function studies are also covered as well as cardiac output, blood volume and blood gases. A long chapter is devoted to a description of the technics and applications of left and right heart catheterization. Study of this important volume of the encyclopedia will give the reader a kaleidoscopic view of the tremendous advances in cardiovascular diagnostic technics achieved in the past two decades. At the same time, great emphasis is rightly placed on the older methods of physical and graphic examinations which have retained their importance despite the more recent innovations in hemodynamic and radiologic technics. Certain chapters reflect years of pioneer study and clinical experience, such as those on physical examination (Cossio), phonocardiography (Luisada), electrocardiography (Massie), vectorcardiography (Grishman), angiocardiography (Castellanos), ballistocardiography (Starr), pulmonary function studies (Motley), cardiac catheterization (Wood, Swan, Björk), cardiac output (Grollman), and blood and heart volumes (Nylin).

Clinical cardiology and therapy are discussed in Volumes 3 and 4. Volume 3 covers congenital, rheumatic, infectious, luetic and coronary heart diseases and disturbances of cardiac rhythm and conduction. Volume 4 continues with hypertension, cor pulmonale, vascular disorders, congestive heart failure and miscellaneous rarer types of cardiovascular diseases. In these two excellent volumes the reader will find authoritative discussions of most of the problems encountered in practice. Emphasis is placed on the clinical manifestations and diagnostic methods in each type of heart disease and on the specific applications of the various graphic and laboratory examinations described in Volume 2.

The vast scope of the material included in these two volumes is demonstrated by the fact that the more common cardiovascular diseases are discussed in several chapters written by different authors, each an expert in his particular field. Although this leads to occasional unevenness in style and depth of coverage it is counterbalanced by completeness. Reference to these chapters with the aid of the excellent table of contents and subject index included in each volume will provide a more complete description of the pathologic, clinical, electrocardiographic, radiologic, catheterization, phonocardiographic and laboratory findings of each type of heart disease than could be found elsewhere.

Treatment, both medical and surgical, as well as special procedures and rehabilitative

measures are well covered, not only in each individual section but also in two final sections on treatment in Volume 4 covering 160 pages. Although the treatment of acute pulmonary edema is fully covered the reviewer believes that more space should have been devoted to the treatment of chronic congestive heart failure. This will probably deserve a separate chapter in future supplements. Another fine feature of the encyclopedia is the complete bibliography at the end of each volume which should serve as an excellent source of selected references for each subject.

The encyclopedia is excellently printed and profusely illustrated with clear figures and photographs. It reflects beautiful craftsmanship on the part of the publisher. Much credit is due to Dr. Luisada without whose tireless and stimulating editorial efforts this monumental work of 2,799 pages could never have been completed, and to the American College of Cardiology for its support of such an educational project. The reviewer believes that this encyclopedia not only is the best and most definitive reference work on cardiovascular diseases in the English language but also will elevate the level of cardiologic knowledge and teaching throughout the world. S. D.

Angiologie: Pathologie, Klinik und Therapie der peripheren Durchblutungsstörungen, by Max Ratschow. Georg Thieme Verlag, Stuttgart, 1959, pp. 831, DM 174, $41.45.

This book replaces the well known German text on peripheral vascular diseases originally published by Ratschow in 1938. Its size alone indicates the great advances which have been made in all aspects of vascular diseases during the past twenty years. Now assisted by twenty-five contributors Ratschow has covered the entire field, including the latest advances in the surgical treatment of vascular diseases.

The division of the subject matter into a general and a special part, as originally adopted by Ratschow, has been retained in this volume. Two-thirds of the book is devoted to general discussions of physiology; pathology, etiology, pathogenesis, diagnosis and general therapy; the remainder of the book deals with "special angiology," i.e., the various clinical entities. As a result of this division, various aspects of individual vascular diseases are discussed in numerous sections of the book, often by different authors with different points of view. The editor states that there may be an advantage in this since such differences of opinion may help the reader to clarify his own thoughts. However, the reviewer believes that this division can be carried too far and, in fact, has been unfortunate inasmuch as it has led to an unnecessary duplication which, in any case, can never be completely avoided in a book written by so many authors. Thus, the reader has to dip into different chapters in order to get a complete picture of any one clinical entity, and this proves very disturbing.

The reviewer agrees with the editor that currently used classifications of vascular disease are far from satisfactory, as organic changes develop in many so-called functional vascular "disorders" and functional disturbances are common in the organic diseases of the vascular system. The classification of vascular diseases into "angio-neuropathies," "angio-organopathies" and "angiolopathies" as proposed by the editor does not, however, help to solve the problem.

There are some excellent chapters, such as the one by Meyer on the inflammatory diseases of the arterial wall and another by Bock on allergic vascular phenomena. The chapter by Hasse on angiographic technic and diagnosis is well written and beautifully illustrated.

Other chapters, such as the one dealing with general therapy, fall short of the standards set by the rest of the book. Perhaps this merely reflects the unsatisfactory state of present day medical treatment of peripheral vascular diseases. Nevertheless, the chapter would have profited by a more critical approach. The reviewer thought that, for instance, the pavex boot and hyperthermia have not stood the test of time and are no longer employed in the treatment of vascular diseases; also, implantation of hypophysis or scarification in cases of peripheral gangrene, although practiced by some native tribes, will probably not find many supporters in this country. In many aspects, therefore, the views expressed in this book deviate from those in accepted Anglo-American texts; however, this may prove stimulating and provocative for those familiar with the subject.

The text is often verbose and requires a good knowledge of German. It is profusely illustrated and the printing is of the usual excellence. Each chapter is provided with a list of references which includes Anglo-American writings.

This book is clearly for the specialist in the field and is not intended for the general physician. ROBERT H. GOETZ, M.D.

Pädiatrischer EKG Atlas, by Wilhelm Heck and Joachim Stoermer. Georg Thieme Verlag, Stuttgart, 1959, pp. 230, DM 78, $18.55.

The introduction and text of the atlas on pediatric electrocardiography is brief and in the reviewer's opinion inadequate. Practically no preparatory discussion of electrophysiology is given; the actual text consists of only seven pages and many tables for minimal and maximal values, deviation, amplitudes, etc.

The atlas section of the book is, on the other hand, excellent. This material is well organized and the legends provide clear and informative descriptions. Many of the cases of congenital heart disease show postmortem confirmations. In almost all records, the six extremity leads (I, II, III, aVR, aVL, aVF) and the six chest leads (V_1 to V_6) had been recorded simultaneously which greatly facilitates their interpretation. Their technical quality is excellent.

The book is valuable to all cardiologists because of the large number of catheterizations presented. The pediatrician and internist will probably feel somewhat lost among the great variability in electrocardiographic configurations unless they consult a text to provide them with a broader explanation of the findings. The book is highly recommended in spite of this probably intentional omission. The printing of text and illustrations is of the very best quality.

ARTHUR GRISHMAN, M.D.

New Methods of Studying Gaseous Exchange and Pulmonary Function, 3rd ed., by Alfred Fleisch. Charles C Thomas, Springfield, 1960, pp. 116, $5.75.

In view of the rapid advances in the field of pulmonary function studies, a new monograph which would help to clarify and put in consolidated form the physiologic basis and clinical application of such studies would be most welcome. Unfortunately, *New Methods of Studying Gaseous Exchange and Pulmonary Function* does not meet this need in its 115 pages.

Dr. Fleisch presents descriptions of (1) the "metabometer," a portable instrument for measuring basal metabolism; (2) basal metabolism and its determination by a "metabocalculator"; (3) a multiple setting constant energy "ergostat"; (4) a pneumotachograph; (5) a "double partition spirometer"; (6) a "totalizer"; (7) an "electrokymograph"; (8) the "metabograph" and (9) the "orthochronograph."

While Dr. Fleisch is to be congratulated on the thoroughness with which he approaches instrumentation, it is unfortunate that the methods presented do not add significantly in theory or practice to those already known and commonly available in this country. The book may be of some interest to students interested in studies of basal metabolism or those who may find some technical interests in Dr. Fleisch's methods. It cannot be enthusiastically recommended to the general reader or to those interested in clinical application of pulmonary function tests. MORTIMER E. BADER, M.D.

RECEIVED FOR REVIEW

All books received will be acknowledged in this column. As space permits, books of special interest will receive more extensive reviews.

Syllabus of Laboratory Examinations in Clinical Diagnosis, edited by Lot B. Page and Perry J. Culver. Harvard University Press, Cambridge, 1960, pp. 580, $12.50.

Respiration. Physiologic Principles and their Clinical Applications, edited by Peter C. Luchsinger and Kenneth M. Moser. C. V. Mosby Company, St. Louis, 1960, pp. 505, $15.75.

Valvular Disease of the Heart in Old Age, by P. D. Bedford and F. I. Carid. Little, Brown & Company, Boston, 1960, pp. 194, $7.50.

Clinical Disorders of the Pulmonary Circulation, edited by Raymond Daley, John F. Goodwin and Robert E. Steiner. Little, Brown & Company, Boston, 1960, pp. 364, $14.00.

Cardiologia. Supplementum II. Vol. 37, edited by Bruno Kisch and W. Löffler. S. Karger Ag., Switzerland, 1960 (Albert J. Phiebig, White Plains, American agent), pp. 288, $10.00.

Congenital Malformation of the Heart, revised edition. Vol. II. **Specific Malformations,** by Helen B. Taussig. Harvard University Press, Cambridge, 1960, pp. 1,049, $17.50.

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College News

President's Column
Robert Prentice Glover, 1913—1961

Robert Prentice Glover, M.D.

THE THIRD President of the College was a surgeon to his finger tips, with a surgeon's uncluttered practicality for the problems that he had to face. I remember very well the first Board meetings over which he presided; our new President was a young man with tremendous energy, a national reputation and what I can describe only as "organizational vision." He was taking the helm when the College was very young and we were all proud of what we had already achieved, with a Roster of 800 members.

Dr. Glover did not seem satisfied. He asked a great many probing questions and I think he frightened the Trustees when he finally summed up his estimate of where he thought the College was, what we had accomplished in each avenue of progress and what plans we could formulate for the future of the College. He gave us all a feeling of urgency and pressure, with a positive direction for growth and expansion that would insure the future of the College in the national picture of cardiology.

Our new President brought from Philadelphia a firm of consulting accountants and a special counsel, a man with broad organizational background. These men combed into the history of the College and checked the efficiency of every function. This group was interested, not in medicine, but in corporate structure and accounting, something the Trustees, as physicians, had found outside their sphere of interest and therefore had discounted in importance. The Trustees Meetings were held twice a month at that time and following the specific recommendations of the special counselor and the auditors it was decided to centralize and consolidate as many functions as possible of the executive work of the College; to gather all the records and books, all the publications, the seals, the charters, the rosters of the Secretary and of the Treasurer, the membership credential blanks, the candidates' records and all the minutes into one Central Executive Office. This was accomplished over a period of months and the wisdom of the plan was not only apparent almost immediately but it must be regarded as responsible for the basic stability of the College as a national corporate structure. This was a thoroughly professional job.

The third annual convention over which Bob Glover presided was held at the Conrad Hilton Hotel in Chicago in May 1954. The program was arranged by Bruno Kisch, Chairman of the Program Committee; a preconvention program was put on by the scientific session of the Chicago Heart Association under the Chairmanship of Clayton Lundy and Walter S. Priest. George Wakerlin, the present Medical

Director of the American Heart Association, was on that Chicago committee. The technical exhibits had been arranged by Seymour Fiske, the banquet speaker was Dr. Austin Smith, Editor of the Journal of the American Medical Association.

It was apparent at this convention that what had happened to the College during Glover's administration was something more than merely the administrative reorganization. The program was studded with great names in American cardiology and each scientific session was a thorough discussion of a single cardiological topic with ample time for questions and answers; and this has been a characteristic of the College programs ever since.

Much as Glover had done for the College during his administration, he was by no means through. After he had passed the gavel to Ashton Graybiel on May 29, 1954, Glover became an active and efficient committee chairman and trustee. He was fired with the mission of the College; he brought in as Fellows many of his eminent colleagues, and as a perennial member of the budget and finance committee he saw to it that the creative work that he had done in stabilizing the administration of the College was not easily disturbed.

Dr. Glover led an unusually active professional life but was never too busy to take on an extra job. Many times when I telephoned his office in Philadelphia and he was absent, his secretary traced his movements and my call might be completed in Houston or Seattle. Bob's voice always came back with a clear and friendly, "What can I do for you now?"

Bob worked out the College budgets year after year and presented them at the Trustees' Meetings. When he was forced to be absent, he never failed to send in a complete written report. All of this is part of the written records in the Archives of the College.

We have lost a Fellow to whom Fellowship meant warmth and active help. If we close ranks and move forward from this point, there will always remain many things to remind us that Robert Prentice Glover had been one of us.

PHILIP REICHERT, M.D., F.A.C.C.
Historian of the College

POST-CONVENTION CRUISE

The program committee has arranged for a gala post-convention cruise to Nassau on the M.S. Italia sailing from New York City at 4 P.M. on May 20, following the closing of the annual meeting. Return date is May 27.

It is hoped to have a group of eighty. Good space is still available.

Reservations for this cruise can be made through Marsh Tours Inc., 630 Fifth Avenue, New York, New York, or through your local travel agent.

FOR ANGINA

Nitroglycerin is the drug of choice for the **ACUTE ATTACK**

'CARDILATE'

may well be chosen for **PROLONGED PROPHYLAXIS**

CLINICAL OPINION

"... the magnitude of the response to 15 mg. ['Cardilate'] was comparable to that following nitroglycerin.... The comparatively prolonged duration of action of erythrol tetranitrate when given sublingually makes it especially valuable for clinical use."[1]

CLINICAL OPINION

"Nitroglycerin and erythrol tetranitrate when administered sublingually are among the most potent of all prophylactic agents available for the treatment of patients with angina pectoris."[2]

CLINICAL OPINION

"Erythrol tetranitrate exhibits an inherent long-acting vasodilating effect. Therefore it is the drug of choice in angina pectoris."[3]

'CARDILATE' brand
Erythrol Tetranitrate Sublingual Tablets

NEW

5 mg., scored

15 mg., scored

Bottles of 100 tablets.

Complete literature available on request.

1. Riseman, J.E.F., *et al.*: Circulation *17*:22 (Jan.) 1958.

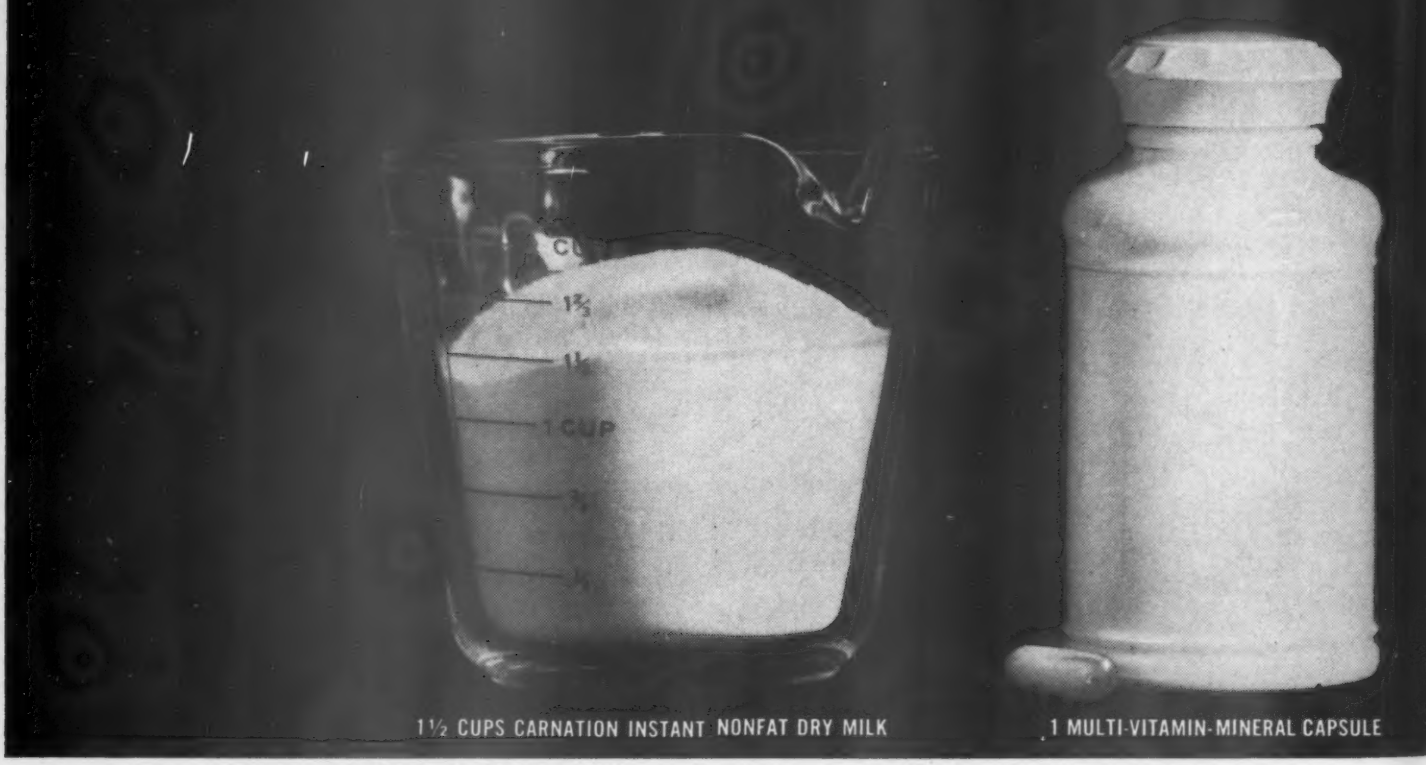
2. Russek, H.I.: Circulation *18*:774 (Oct.) 1958.

3. Hirshleifer, I., *et al.*: Scientific Exhibit, A.M.A., Atlantic City, N. J., June, 1959.

BURROUGHS WELLCOME & CO. (U.S.A.) INC., Tuckahoe, New York

ANNOUNCING: THE CARNATION WEIGHT REDUCTION PLAN

AN EFFECTIVE MEAL-REPLACEMENT FORMULA DIETING PATIENTS CAN MAKE AT HOME—FOR ONLY 44¢ A DAY



1½ CUPS CARNATION INSTANT NONFAT DRY MILK

1 MULTI-VITAMIN-MINERAL CAPSULE

THE CARNATION WEIGHT REDUCTION PLAN

This Plan is a *new* meal-replacement weight reduction regimen based on delicious milk products plus a standard multi-vitamin-mineral preparation.

Carnation's nutritionally-balanced meal-replacement Plan supplies 1000 calories and 70 grams of high quality protein.

EASY FOR PATIENTS TO MAKE

TAKE 1 standard multi-vitamin-mineral preparation each day.

MIX one day's supply (4 glassfuls) of Carnation Plan Formula by stirring together in a container larger than a quart:

1½ cups CARNATION INSTANT NONFAT DRY MILK

1 quart WHOLE MILK

If desired, flavor with instant coffee or a variety of extracts.

Chocolate flavoring adds 30 calories per teaspoonful.

OR for a Single Glass: Mix a generous ⅓ cup Carnation Instant with 1 cup whole milk.

COSTS ONLY 44¢ A DAY

The total expense for the Carnation Weight Reduction Plan —including the multi-vitamin-mineral preparation—is 44¢ a day. Compare this to the price dieters pay for the largest-selling pre-mixed product.

TASTES NATURALLY DELICIOUS

Because the Carnation Plan Formula is based on fine, pure dairy products, it has a fresh milk flavor. Patients can vary this flavor by simply adding 3 to 4 teaspoons of instant coffee, or 1½ teaspoons of any of their favorite extracts, like vanilla, per quart.

AN EFFECTIVE, FLEXIBLE PLAN

The Carnation Weight Reduction Plan provides balanced nutrition. Providing 1000 calories a day, the Plan gives the dieter 70 grams of high-quality, hunger-appeasing protein. This concentration of protein helps satisfy the appetite, and at the same time, keeps up the dieter's energy. The Plan meets the Daily Adult Requirement for all vitamins and minerals with established minimums.

1 QUART FRESH, WHOLE MILK

Four glasses of the Carnation Weight Reduction Formula and the vitamin-mineral supplement* answer the Minimum Daily Adult Requirement for all known vitamins and minerals. Besides 70 grams of high-quality protein, 100 grams of carbohydrate, and 36.8 grams of fat, the Carnation Weight Reduction Plan provides:

		Multiples of M.D.R.
Vitamin A	6540 Units	1.3
Vitamin D	500 Units	1.2
Ascorbic Acid (C)	76 Mg.	2.5
Thiamin (B_1)	5.77 Mg.	5.7
Riboflavin (B_2)	8.6 Mg.	7
Niacinamide	16.8 Mg.	1.6
Iron	11.8 Mg.	1.1
Calcium	2.7 Gm.	3
Phosphorus	2.1 Gm.	2.8
Iodine	0.56 Mg.	5.6
Pyridoxine (B_6)	1.42 Mg.	**
Ca Pantothenate	11.8 Mg.	**
Vitamin B_{12}	2.0 Mcg.	**
Vitamin E	10.6 Units	**
Sodium	1.1 Gm.	**
Potassium	3.0 Gm.	**
Manganese	1.0 Mg.	**
Magnesium	1.3 Gm.	**
Copper	1.6 Mg.	**
Zinc	8.0 Mg.	**
Calories	1000	

**Calculations are based on a standard multi-vitamin-mineral supplement, 1½ cups Carnation Instant Nonfat Dry Milk, and 1 quart of whole milk.*

***M.D.R. (Minimum Daily Requirement) has not been established.*

The physician prescribes the multi-vitamin-mineral preparation to supply the vitamin-mineral elements outside the basic food drink. The physician may also wish to vary the number of meals the dieter replaces with the Carnation Plan Formula and the number of days the patient stays on the regimen. In this way the physician is given the opportunity to adjust the regimen of the dieter to suit the needs of *each* individual patient.

BULK—TO PROTECT AGAINST CONSTIPATION

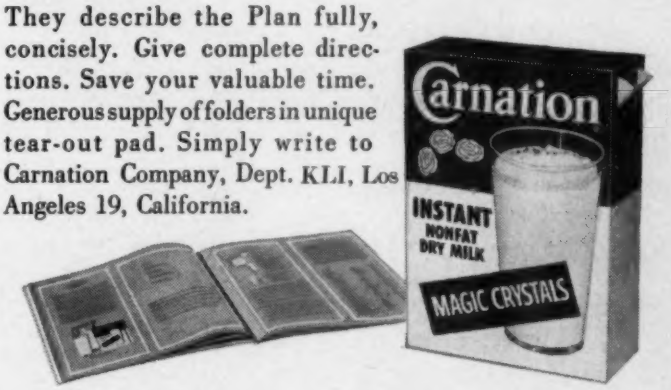
Dieters can snack with low-calorie vegetables and greens like celery, cucumbers, radishes, green pepper, lettuce. These snacks are welcomed by the dieter, and they aid regularity. Coffee and tea (without sugar and cream) may be used. Plenty of water is generally recommended.

FOR *ALL* DIET-CONSCIOUS PATIENTS

Carnation Nonfat Dry Milk can be recommended apart from a meal-replacement diet. All patients interested in weight control can get important protein, calcium, and B-vitamins the low-calorie way. Only 81 calories in an 8-ounce glass of regular Carnation Instant Nonfat Dry Milk.

• FOR CONVENIENCE: CARNATION WEIGHT REDUCTION PLAN FOLDERS FOR YOUR PATIENTS

They describe the Plan fully, concisely. Give complete directions. Save your valuable time. Generous supply of folders in unique tear-out pad. Simply write to Carnation Company, Dept. KLI, Los Angeles 19, California.



Carnation Company

"First in the hearts"
of cardiac patients

A.C.M.I.
CARDIAC CATHETERS

A.C.M.I. was the first to introduce nylon woven catheters in the United States — originally for ureteral use — later for cardiac catheterization.

A.C.M.I.'s nylon woven cardiac catheters are preferred for smoothness combined with flexibility. Lengths: 30 cm. to 150 cm. Thin-walled, radiopaque.

A.C.M.I.'s polyethylene cardiac catheters provide a smoother and larger lumen for collection of blood samples and the rapid injection of contrast media. Other types too are under development.

A triumph of technical skill — all A.C.M.I. cardiac catheters have earned the confidence of the medical profession through their consistently superior quality.

Nylon woven cardiac catheters

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American Cystoscope Makers, Inc.

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Protects the angina patient better than vasodilators alone

Unless the coronary patient's ever-present anxiety about his condition can be controlled, it can easily induce an anginal attack or, in cases of myocardial infarction, can delay recovery.

This is why Miltrate gives better protection for the heart than vasodilators alone in coronary insufficiency, angina pectoris and postmyocardial infarction.

Miltrate contains PETN (pentaerythritol tetranitrate), acknowledged as basic therapy for long-acting vasodilation. . . .

What is more important—Miltrate provides Miltown, a tranquilizer which, unlike phenobarbital, relieves tension in the apprehensive angina patient without inducing daytime fogginess.

Thus, your patient's cardiac reserve is protected against his fear and concern about his condition; his operative arteries are dilated to enhance myocardial blood supply—and he can carry on normal activities more effectively since his mental acuity is unimpaired by barbiturates.

REFERENCES: 1. Ellis, L. B. *et al.:* Circulation *17*:945, May 1958. 2. Friedlander, H. S.: Am. J. Cardiol. *1*:395, Mar. 1958. 3. Riseman, J.E.F.: New England J. Med. *261*:1017, Nov. 12, 1959. 4. Russek, H. I. *et al.:* Circulation *12*:169, Aug. 1955. 5. Russek, H. I.: Am. J. Cardiol. *3*:547, April 1959. 6. Tortora, A. R.: Delaware M. J. *30*:298, Oct. 1958. 7. Waldman, S. and Pelner, L.: Am. Pract. & Digest Treat. *8*:1075, July 1957.

Supplied: Bottles of 50 tablets. Each tablet contains 200 mg. Miltown and 10 mg. pentaerythritol tetranitrate.

Dosage: 1 or 2 tablets q.i.d. *before meals* and at bedtime, according to individual requirements.

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Miltrate®

Miltown® (meprobamate) + PETN

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A Report

A recent independent study made by a professional consultant found in 10 outstanding college food, nutrition, and health textbooks that, without exception, among other breakfasts, a basic cereal breakfast, mostly based on the Iowa Breakfast Studies* appeared in every textbook examined.

These studies, originated in 1948 by the College of Medicine at the State University of Iowa, demonstrated that an adequate breakfast was beneficial, whereas previously only opinion prevailed.

**A Summary of the Iowa Breakfast Studies, published by Cereal Institute, Inc., May 1, 1957.*

CEREAL INSTITUTE, INC.
135 South LaSalle Street, Chicago 3

A research and educational endeavor devoted to the betterment of national nutrition

cereals are low in fat

Introducing new therapy for

hypertension and congestive failure

lowers blood pressure
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Now the most widely prescribed diuretic-antihypertensive, hydrochlorothiazide, is combined with the most widely prescribed tranquilizer, meprobamate. It is called "Miluretic", and constitutes new therapy for hypertension and congestive failure — *especially when emotional factors complicate treatment.*

What does Miluretic do? Both components are of proven value in the management of hypertension. In congestive failure, Miluretic provides smooth, continuous diuresis. But Miluretic's biggest advantage is that it tranquilizes hypertensive and edematous patients safely and quickly—*a boon to the physician whose patients' emotional reaction to their condition complicates therapy.* Unlike Rauwolfia compounds, Miluretic does not cause depression or nasal congestion.

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MILTOWN® + HYDROCHLOROTHIAZIDE

Composition: 200 mg. Miltown (meprobamate, Wallace) + 25 mg. hydrochlorothiazide

Dosage: For hypertension, 1 tablet four times a day. For congestive failure, 2 tablets four times a day.

Supplied: Bottles of 50 white, scored tablets

Available at all pharmacies

Write for samples and complete literature to

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"nutrition . . . present as a modifying or complicating factor in nearly every illness or disease state."[1]

Theragran®

SQUIBB VITAMINS FOR THERAPY

clinically-formulated and potency-protected vitamins for your patients with cardiac disease who need therapeutic vitamin support

"Who can say, for example, whether the patient chronically ill with myocardial failure may not have a poorer myocardium because of a moderate deficiency in the vitamin B-complex? Something is known of the relationship of vitamin C to the intercellular ground substance and repair of tissues. One may speculate upon the effects of a deficiency of this vitamin, short of scurvy, upon the tissues in chronic disease."[2]

Each Theragran supplies the essential vitamins in truly therapeutic amounts:

Vitamin A	25,000 U.S.P. Units
Vitamin D	1,000 U.S.P. Units
Thiamine Mononitrate	10 mg.
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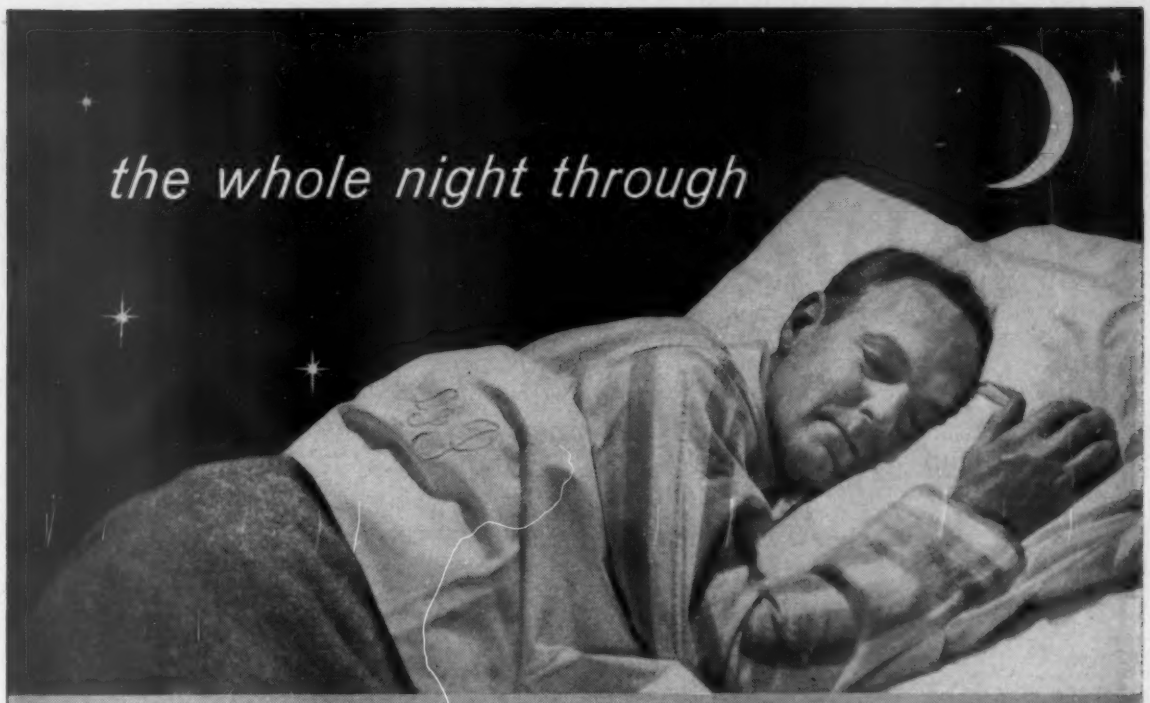
Pyridoxine Hydrochloride	5 mg.
Calcium Pantothenate	20 mg.
Vitamin B_{12}	5 mcg.

For full information see your Squibb Product Reference or Product Brief.

1. Youmans, J. B.: Am. J. Med. **25**:659 (Nov.) 1958.
2. Kampmeier, R. H.: Am. J. Med. **25**:662 (Nov.) 1958.

SQUIBB *Squibb Quality—the Priceless Ingredient*

'Theragran'® is a Squibb Trademark



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QUINAGLUTE®

DURA-TAB S.M.®

exclusive oral Sustained Medication*
Quinidine Gluconate (5 gr.)

maintains normal sinus rhythm in cardiac arrhythmias

Dosage with Quinaglute Dura-Tab S.M. is "relatively simple."[1] One dose q. 12 h. maintains effective, uniform quinidine blood levels around the clock, all night, all day. There are no valleys in blood concentration where arrhythmias tend to recur.

Better tolerated — because quinidine gluconate is ten times as soluble as quinidine sulfate—and easier on the g.i. tract. And because only a fraction of the daily dose of Quinaglute Dura-Tab S.M. is released in the stomach.

A quinidine of choice in control of atrial fibrillation, flutter, premature contraction, auricular tachycardia.[1-4] Bottles of 30, 100 and 250.

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Also available: INJECTABLE QUINAGLUTE
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1. Bellet, S., Finkelstein, D., and Gilmore, H.: A.M.A. Arch. Int. Med. 100:750, 1957.
2. Bellet, S.: Amer. Heart J. 56:479, 1958.
3. Finkelstein, D.: Penn. Med. J. 61:1216, 1958.
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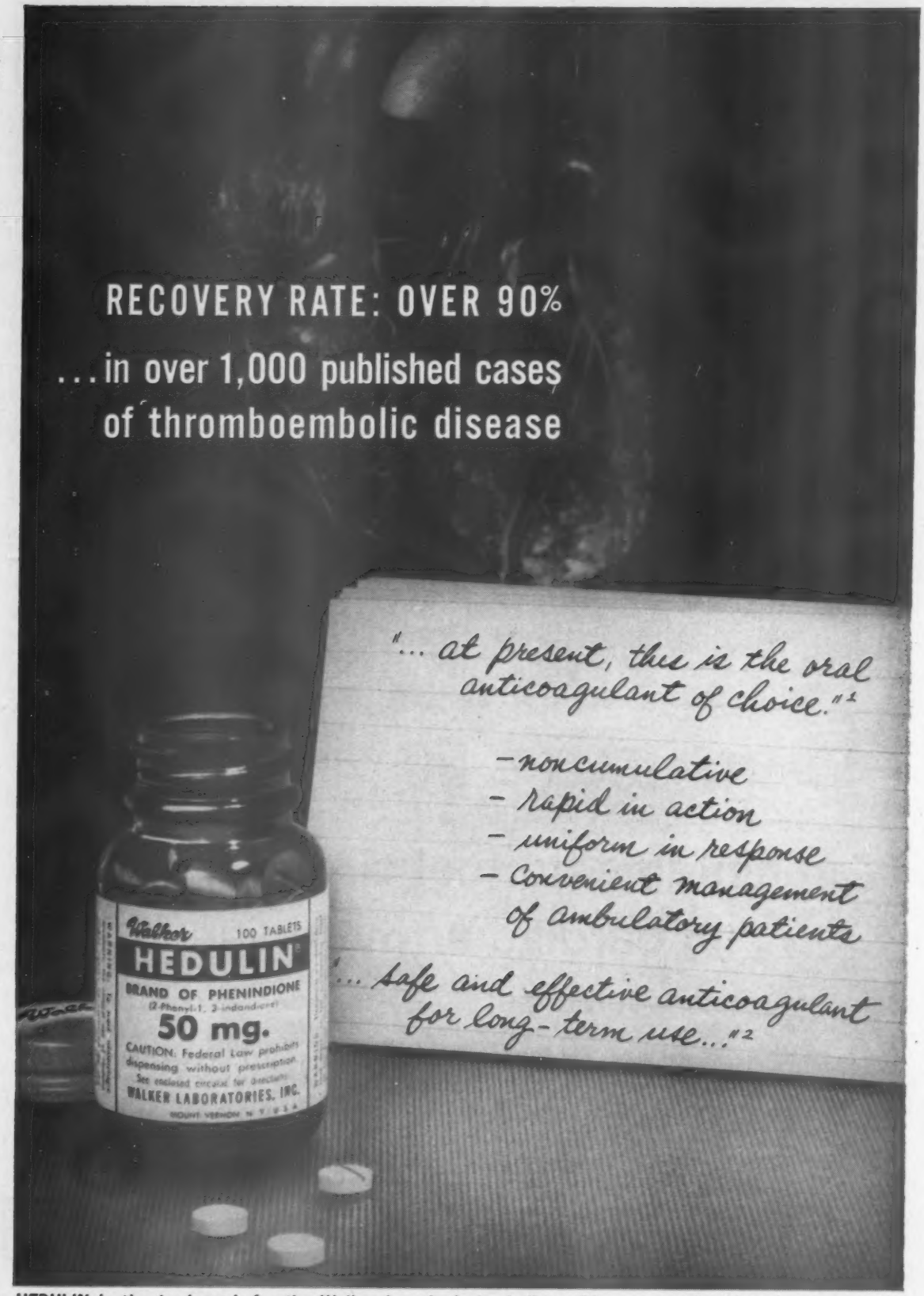
RECOVERY RATE: OVER 90%
... in over 1,000 published cases of thromboembolic disease
"... at present, this is the oral anticoagulant of choice."[1]
- noncumulative
- rapid in action
- uniform in response
- convenient management of ambulatory patients
... safe and effective anticoagulant for long-term use..."[2]
Walker
100 TABLETS
HEDULIN
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CAUTION: Federal Law prohibits dispensing without prescription
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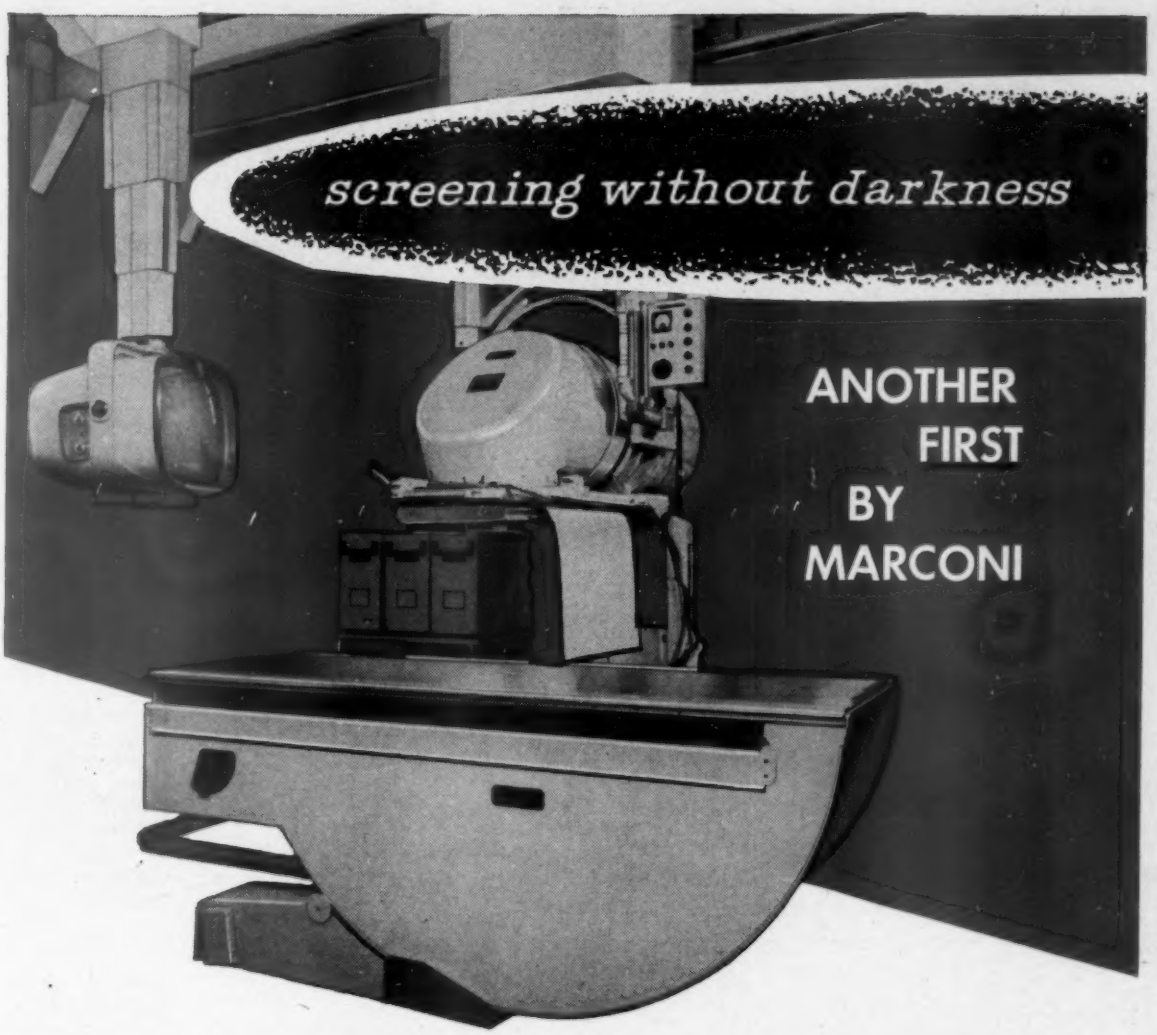
HEDULIN is the trademark for the Walker brand of phenindione. 50 mg. scored tablets for therapeutic use; 20 mg. scored tablets for prophylactic use. Bottles of 100 and 1,000. For more detailed information and a clinical trial supply of Hedulin, write to Walker Laboratories, Inc., Mount Vernon, N. Y.

1. Breneman, G. M., and Priest, E. McC.: Am. Heart J. 50:129 (July) 1955. 2. Tandowsky, R. M.: Am. J. Cardiol. 3:551 (April) 1959.



The revolutionary MARCONI IMAGE AMPLIFIERS are being introduced for the first time on the North American Continent.

SCREENING WITHOUT DARKNESS by the use of a 12" FLAT SCREEN is an entirely new approach to the problem of improving the information factor of fluoroscopic images. The use of the television image orthicon tube opens up enormous fields of application.

- Amplifier will operate four monitors at the same time. Useful for consultations and in teaching hospitals.
- The cine camera facility makes it possible for the first time to produce continuous record of the large fluoroscopic image at doses tolerable to the patient.
- Cine recording is done by using fluoroscopic Ma . . . can be used on 16 or 35 m.m. films as well as 100 m.m. spot films.
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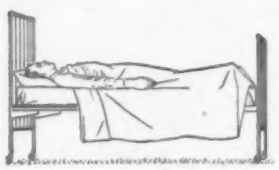
a new agent to lyse thrombi

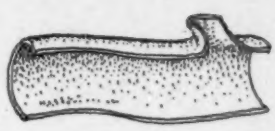
THROMBOLYSIN®

LYOVAC® FIBRINOLYSIN (HUMAN)

Results of therapy	Bed rest	
Effect on intravascular thrombi		Clot may form permanent obstruction to blood flow. New clots may form.
Effect on pulmonary emboli		Sudden death from pulmonary embolism is an ever-present hazard. One or more nonfatal pulmonary emboli may result in irreversible lung damage or secondary pneumonia.
Effect on duration of illness and convalescence		Weeks of hospitalization or bed rest at home are commonly required in the management of thrombophlebitis, phlebothrombosis, pulmonary embolism, and arterial thrombosis.
Frequency and severity of postphlebitic syndrome		Chronic leg swelling, severe secondary varicose veins, and leg ulcers are common sequelae.

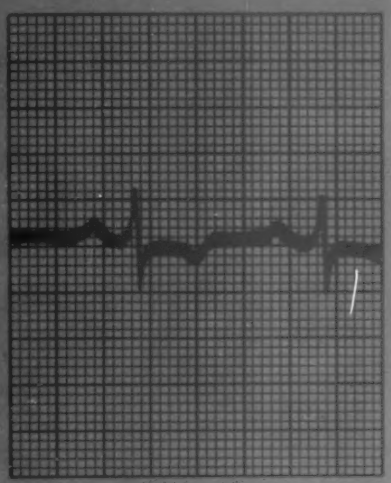
In thrombophlebitis, phlebothrombosis, pulmonary embolism, and certain arterial thrombi*, THROMBOLYSIN makes possible
• lysis of formed clots • reduced mortality and morbidity, shortened hospitalization
• reduced incidence of postphlebitic complications
usually fewer severe untoward reactions, such as fever, chills, or malaise;
higher degree of safety; greater, more predictable potency.

Supply: **Each vial contains 50,000 MSD units.**
***Arterial thrombosis with the exception of cerebral or coronary thrombosis.**

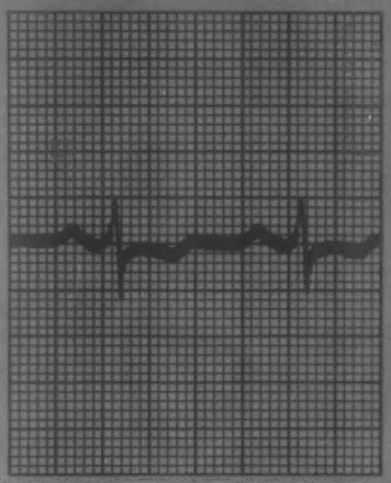
Anticoagulant + Bed rest	THROMBOLYSIN + Anticoagulant + Bed rest
Anticoagulants cannot remove formed clot. However, they may help prevent its extension and may minimize formation of new clots.	 Recently formed intravascular clots are usually lysed rapidly and the formation of new clots may be inhibited. Circulation is usually restored and maintained, with rapid symptomatic relief.
The careful use of anticoagulants may reduce the occurrence of pulmonary emboli.	The incidence and severity of pulmonary emboli should be greatly reduced since THROMBOLYSIN may dissolve thrombi before they can become emboli.
Thromboembolic illness and convalescence may be shortened.	A reduction may be observed in the duration of hospital stay, bed rest, and convalescence.
The incidence and severity of the postphlebitic syndrome may be reduced.	Postphlebitic complications may be prevented or minimized.

For additional information, write to Professional Services, Merck Sharp & Dohme, West Point, Pa.
MERCK SHARP & DOHME, DIVISION OF MERCK & CO., INC., WEST POINT, PA.
THROMBOLYSIN IS A TRADEMARK OF MERCK & CO., INC.

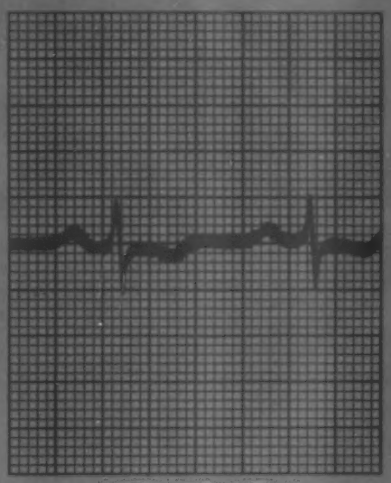
for overweight cardiacs/hypertensives... Rx the anorexic with no reported contraindications



Lead II: at rest.



Lead II: 1½ minutes after 10 mg. TENUATE i.v.—equivalent to 100 mg. oral dose (4 times the recommended oral dose).



5 minutes after injection.

with Tenuate, ECG fluctuation is insignificant[1]

TENUATE

(diethylpropion)

hunger control with less than 1% CNS stimulation[2-8]

TENUATE suppresses appetite with unique advantages for "special risk" patients: no effect on heart rate, blood pressure, pulse or respiration,[1] no alteration of BMR.[2]

Dosage: One 25 mg. Tablet one hour before meals, or 1 *new* TENUATE DOSPAN Tablet (75 mg.) daily, in midmorning, swallowed whole. An additional 25 mg. Tablet may be taken in midevening to control nighttime hunger.

Supply: TENUATE Tablets (25 mg. each), bottles of 100 and 1000; TENUATE DOSPAN Tablets (75 mg. each), bottles of 100.

References: 1. Alfaro, R. D.; Gracanin, V. and Schlueter, E.: J. Lancet *(in press)*. 2. Huels, G.: Michigan Acad. Gen. Pract. Symposium, Detroit, 1959. 3. Horwitz, S.: Personal communication, 1959. 4. Spielman, A. D.: Michigan Acad. Gen. Pract. Symposium, Detroit, 1959. 5. Ravetz, E.: Michigan Acad. Gen. Pract. Symposium, Detroit, 1959. 6. Decina, L. J.: Exper. Med. & Surg. *(in press)*. 7. Scanlan, J. S.: Personal communication, 1959. 8. Kroetz and Storek: Personal communication, 1959.

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10 TO 12 HOUR HUNGER CONTROL WITH 1 TABLET

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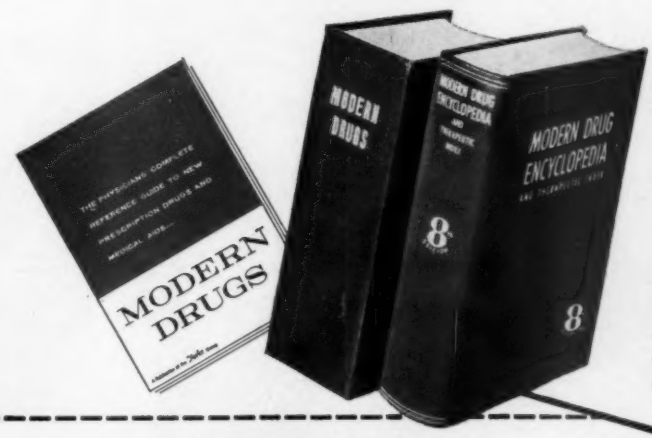

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Abbott Laboratories
Enduron*.....*Inserting facing page* 16

American Cystoscope Makers, Inc.
Cardiac Catheters..... 38

Amfre-Grant, Inc.
Corovas*..... 15

Burroughs Wellcome & Co. (U.S.A.), Inc.
Cardilate*..... 35
Lanoxin*..... 23

Carnation Company
Instant Milk.....36–37

Cee Bee Services
Image Amplifiers..... 45

Cereal Institute, Inc.
Nutrient..... 40

Ciba Pharmaceutical Products, Inc.
Serpasil-Apresoline*..... 21

Endo Laboratories
Coumadin*..... 22

Geigy Company
Hygroton*..... 50
Sintrom*/Tromexan*..... 27

Ives-Cameron Company
Cyclospasmal*..... 54
Isordil*..... 30

Lederle Laboratories, Div. American Cyanamid Co.
Diamox*..... 14

Thos. Leeming & Co., Inc.
Clarin*..... Third Cover

Eli Lilly & Company
Crystodigin*..... 34

Merck Sharp & Dohme, Div. Merck & Co., Inc.
Aramine*.....32–33
Thrombolysin*.....46–47

The Wm. S. Merrell Company
Mer/29*.....24–25
Tenuate*..... 48

Minneapolis-Honeywell
Electronic Medical Equipment.....28–29

Ortho Pharmaceutical Corp.
Actase*.....Second Cover

Pitman-Moore, Div. of Allied Laboratories, Inc.
Emdee Margarine..... 20

Riker Laboratories, Inc.
Rauwiloid*.....Fourth Cover

Roche Laboratories, Div. of Hoffmann-La-Roche, Inc.
Marplan*..... 4

Sanborn Company
Cardiac Equipment..... 16

Schering Corporation
Naqua*..... 31

G. D. Searle & Co.
Aldactazide*..... 1

E. R. Squibb & Sons, Div. of Mathieson Chemical Corp.
Pronestyl*..... 12
Rautrax-N..... 53
Theragran*..... 42

Charles C Thomas, Publisher
Medical Books..... 19

Walker Laboratories, Inc.
Hedulin*..... 44
Nicalex*..... 2

(Continued on next page)

*** Complete description of starred drugs will be found in MODERN DRUGS and THE MODERN DRUG ENCYCLOPEDIA**

Wallace Laboratories
Deprol* 26
Miltown* 8
Miltrate* 39
Miluretic* 41

Warner-Chilcott Laboratories
Peritrate* 10

Winthrop Laboratories
Dilcoron* 6

Wynn Pharmacal Corp.
Quinaglute* 43

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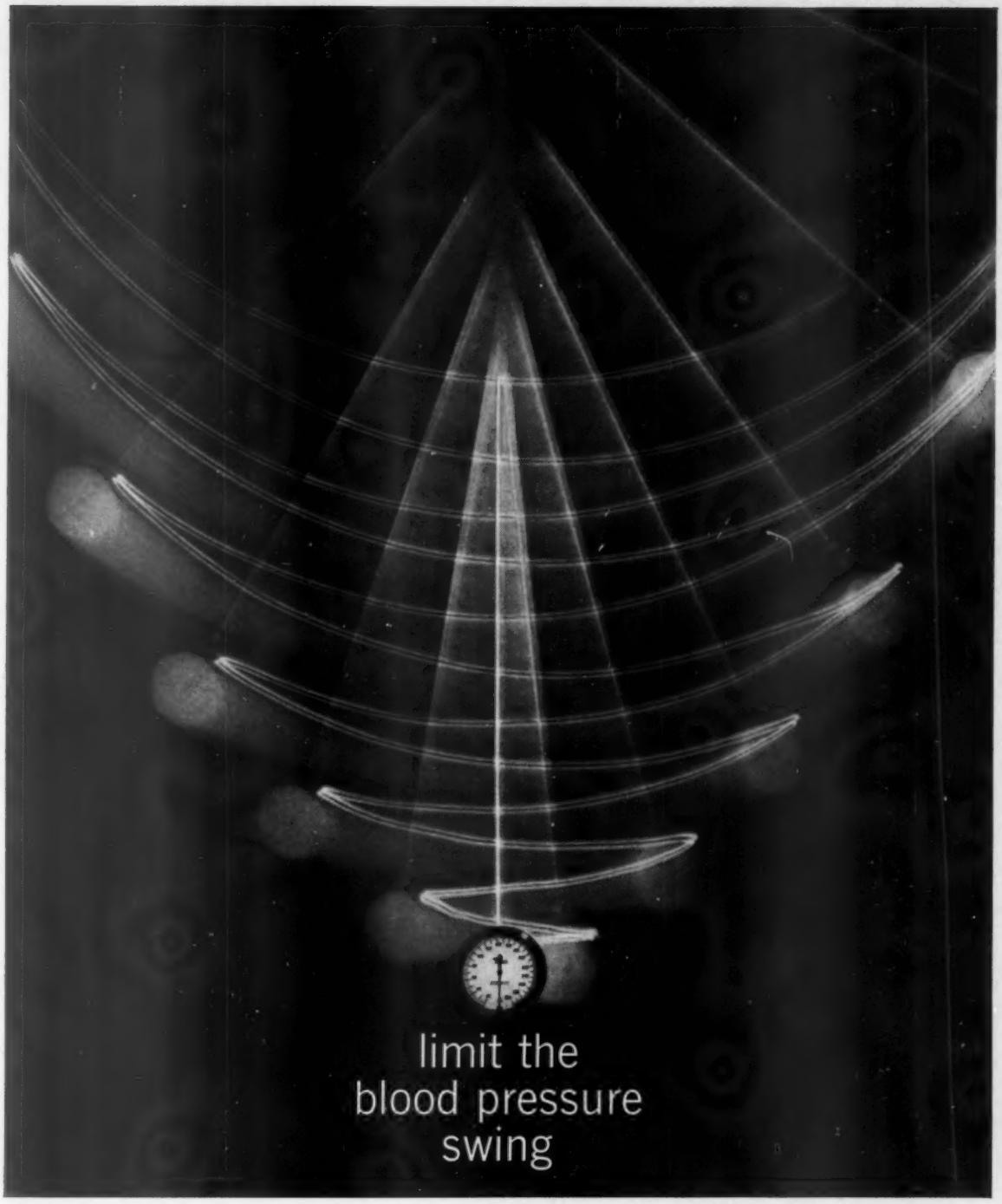

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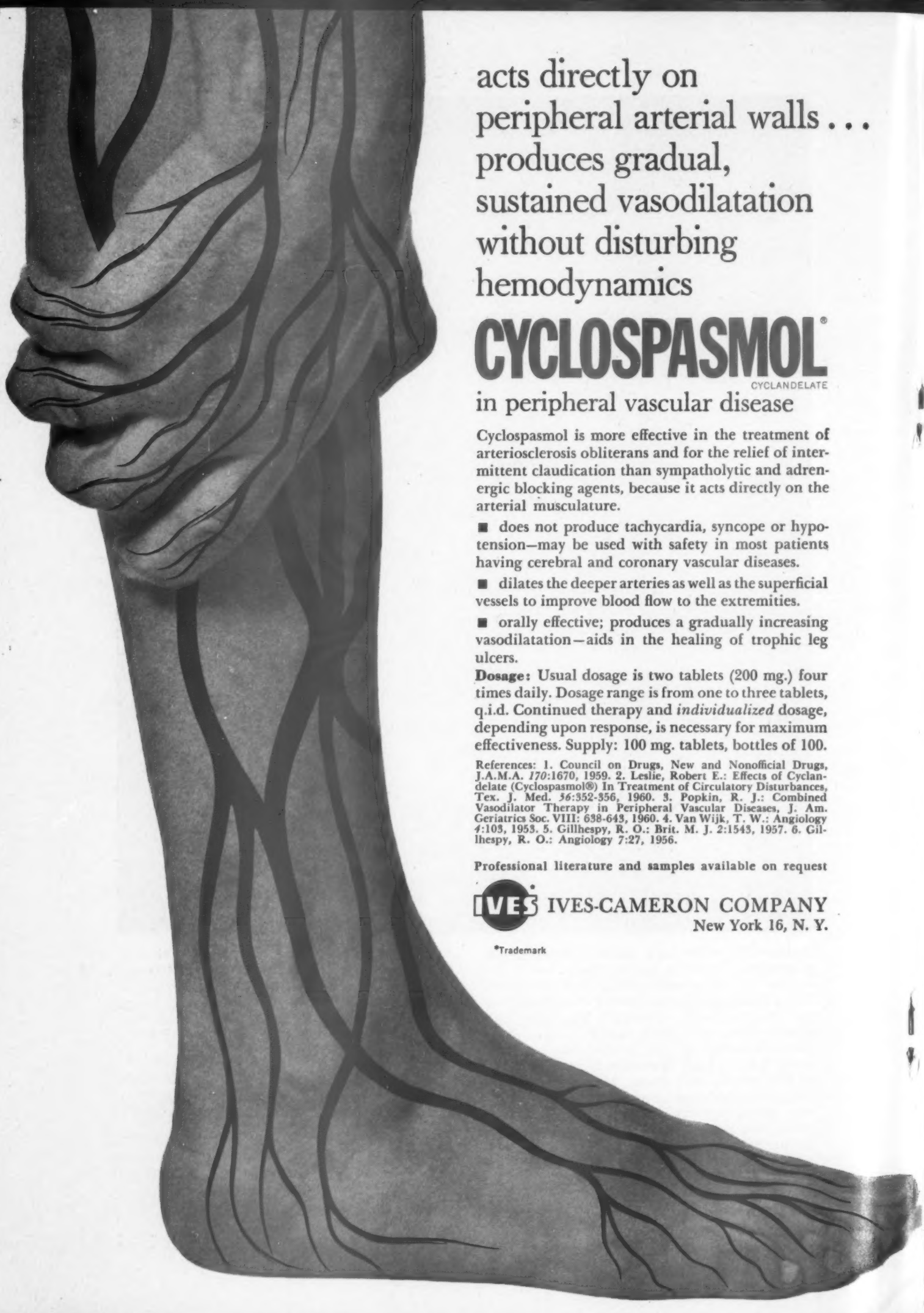

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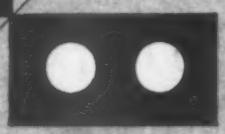

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